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Original Article

Effects of radical cystectomy combined with GC chemotherapy in the treatment of invasive bladder cancer and its influence on the incidence of adverse reactions

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Abstract: Objective: To explore the efficiency of radical cystectomy combined with GC chemotherapy in the treatment of invasive bladder cancer and its influence on the incidence of adverse reactions. Methods: The clinical data of 120 patients with invasive bladder cancer admitted to our hospital from February 2015 to February 2016 were retrospectively analyzed. According to different treatment methods, they were equally divided into two groups. The experimental group (n=60) was treated with radical cystectomy combined with GC chemotherapy. The control group (n=60) was treated with bladder-preserving comprehensive treatment (transurethral bladder tumor resection + internal iliac artery infusion chemotherapy + intravesical infusion chemotherapy). The short-term efficiency, adverse reactions, long-term treatment indicators, survival, surgical indicators, and quality of life were compared between the two groups. Results: The two groups showed similar objective remission rate and disease control rate (P>0.05). Both groups of patients had different degrees of hematological toxicity and non-hematological toxicity, but no severe systemic organ toxicity. Fewer patients in the experimental group experienced anemia and fever compared with the control group (P<0.05). The incidence of recurrence, hydronephrosis, and metastasis in the experimental group was significantly lower than that in the control group (P<0.05). The experimental group showed a higher 3-year survival rate than the control group (86.7% *vs* 75.0%), with no statistical difference between the two groups (P>0.05). The experimental group obtained a significantly higher 5-year survival rate than that of the control group (70.0% *vs* 51.7%) (P<0.05). The experimental group outperformed the control group in terms of surgical indicators (P<0.001). The two groups had similar quality of life scores after the 5-year follow-up (P>0.05). Conclusion: Radical cystectomy combined with GC for the treatment of invasive bladder cancer reduces the incidence of adverse reactions and enhances the 5-year survival of patients, with a promising long-term efficiency.

Keywords: Radical cystectomy, GC chemotherapy, invasive bladder cancer

Introduction

Bladder cancer is a common clinical malignant tumor of the urinary system. According to the 2002 *Chinese Cancer Survey Report*, the incidence of bladder cancer was well below 0.01% [1], which is far below that in western developed countries [2]. The past two decades have witnessed a steady increase in the incidence of bladder cancer in China. Most cases were well- or moderate-differentiated non-muscle invasive bladder cancer at diagnosis [3, 4]. Ten percent progressed to muscle invasive bladder cancer [5]. This disease is rapidly progressive and highly malignant. Patients remain at risk of recurrence and metastasis after systemic therapy with a poor prognosis [6, 7].

Radical cystectomy combined with pelvic lymph node dissection is widely performed in clinical practice to treat bladder cancer. As the standard treatment option for high-grade invasive bladder cancer, radical cystectomy combined with pelvic lymph node dissection can achieve bladder tumor eradication and long-term tumor-free survival of patients. The current surgical protocol has been criticized for its drawbacks. The 5-year survival of patients was 55%-68%. Metastases were found in 40% of patients within 2 years, mostly due to micro-metastases at

the time of diagnosis [7]. It had a long postoperative recovery time and multiple surgical complications. It is particularly important to explore appropriate treatment options to achieve bladder preservation surgery with the same efficacy as radical cystectomy. Neoadjuvant chemotherapy, such as gemcitabine + cisplatin (GC) chemotherapy, with well-established safety and efficacy, has captured the attention of the academic community [8-10]. It has been reported that patients with T2-T4a operable bladder tumors without metastasis are at a low risk of bladder tumor recurrence, lymph node metastasis, and distant metastasis after effective neoadjuvant chemotherapy and bladder preservation surgery. The 5-year survival rate reached 57%, which is like the 5-year survival of patients who underwent radical cystectomy combined with pelvic lymph node dissection [10, 11].

To fully explore the difference in the efficiency between radical cystectomy combined with GC chemotherapy and bladder preservation comprehensive treatment, 120 patients were enrolled as research subjects in the study. The results are summarized as follows. This study investigated the efficacy of neoadjuvant chemotherapy and transurethral bladder tumor resection + internal iliac artery perfusion chemotherapy + bladder perfusion chemotherapy and compares it with that of radical surgery, with the aim of obtaining more reliable data for clinical treatment.

Materials and methods

Research design

This study was conducted in our hospital from February 2015 to February 2016. The aim was to explore the efficacy of radical cystectomy combined with GC chemotherapy in the treatment of invasive bladder cancer and its influence on the incidence of adverse reactions.

Recruitment of research subjects

A total of 120 patients were enrolled and divided into the experimental group (n=60) and the control group (n=60) according to different treatment methods. The baseline data of the two groups were collected and no statistical difference was found between the two groups (P>0.05), as shown in **Table 1**.

Inclusion criteria: (1) Patients who were diagnosed with invasive bladder cancer by imaging and pathological examinations; (2) Patients with complete clinical data; (3) Patients who underwent local lesion excision after the first neoadjuvant chemotherapy; (4) Patients with tumor stage of TNM 2-4.

Exclusion criteria: (1) Patients who were unable to communicate due to hearing impairment, language impairment, unconsciousness, or mental illness; (2) Patients who withdrew from the treatment, died, changed treatment plans, or were lost in follow-up; (3) Patients with superficial bladder cancer, benign bladder tumors or other malignancies that had metastasized to the bladder; (4) Patients with incomplete clinical data; (5) Patients who had received chemotherapy, radiotherapy, surgery, biologic therapy, immunotherapy, or other treatment prior to enrollment; (6) Patients with lymphovascular or distant metastases; (7) Patients who had adverse events or serious adverse events; (8) Patients whose condition deteriorated during the experiment; (9) Patients who had some serious co-morbidities or complications.

Moral considerations

This study complies with the guidelines laid down in the *Declaration of Helsinki* [12] and was approved by the hospital's ethical review committee (2014-20-11). After recruitment, the patients were informed of the purpose, significance, content, and confidentiality of the study and signed an informed consent form.

Methods

The experimental group underwent radical cystectomy combined with GC chemotherapy: (1) Radical cystectomy: the patient was placed in the lithotomy position and intubated under general anesthesia. The bladder was freed and completely removed during surgery. In male patients, the prostate and seminal vesicles were also removed. In female patients, the uterus and bilateral appendages were removed, the enlarged pelvic lymph nodes were cleared, and urethral reconstruction was performed according to the actual situation of the patients. (2) GC chemotherapy regimen: ① After surgery, the chest radiographs and blood vessel images of patients were reviewed. GC chemotherapy was performed when the indicators of the chest

Table 1. Comparison of general information

Groups	Experimental group (n=60)	Control group (n=60)	χ^2/t	P
Gender			0.040	0.841
Male	42	43		
Female	18	17		
Age (year)				
Range	52-76	54-74		
Mean age	64.21±2.65	64.26±2.54	0.106	0.916
Mean weight (kg)	58.11±2.10	58.23±2.05	0.317	0.752
BMI (kg/m^2)	22.36±1.23	22.32±1.20	0.180	0.857
Number of tumors			0.046	0.831
Single	45	46		
Multiple	15	14		
Pathological grade			0.035	0.852
High	24	23		
Low	36	37		
Pathological type				
Urothelial Carcinoma	55	54	0.100	0.752
Squamous cell carcinoma	3	4	0.152	0.697
Adenocarcinoma	2	2	0.000	1.000
Place of residence			0.034	0.853
Urban	25	26		
Rural	35	34		
Monthly income (CNY)			0.033	0.855
≥4000	28	29		
<4000	32	31		
Habit of life				
Smoking	35	34	0.034	0.853
Drinking	30	32	0.134	0.715
Educational background			0.134	0.715
High school or below	30	32		
College or above	30	28		

radiographs and blood vessel images returned to preoperative levels. Liver function, kidney function, and renal function were reviewed 24 hours before drug administration. ② 1000 mg/m^2 Gemcitabine (Qilu Pharmaceutical Hainan Co., Ltd., SFDA Approval No. H20113286) was diluted in 250 mL of normal saline and administered to patients by intravenous injection for 30 minutes on days 1 and 8 of each treatment cycle. 30 mg/m^2 cisplatin (Guizhou Hanfang Pharmaceutical Co., Ltd., SFDA Approval No. H20020272) diluted in 250 mL of normal saline were intravenously infused within 60-90 minutes on days 2, 3, and 4. ③ Patients were routinely administered dexamethasone sodium phosphate injection (Guizhou Tiandi Pharmaceutical Co., Ltd., SFDA Approval No. H52020477) intravenously before instillation, and ondansetron after instillation (Ningbo Tianheng Pharmaceutical Co., Ltd., SFDA Approval No. H20051692). Antiemetics (8 mg), normal saline solution, and 1000 mL dextrose sodium chloride injection (Yichang Sanxia Pharmaceutical Co., Ltd., SFDA Approval No. H20123143) were administered to patients on the day of cisplatin instillation. Before the intravenous injection of cisplatin, patients were treated with an IV infusion of 125 mL Mannitol (Hubei Duorui Pharmaceutical Co., Ltd., SFDA Approval No. H20123079) to reduce the toxicity of cisplatin. ④ The blood routine of patients was examined every week during chemotherapy, and the adverse reactions were recorded. The treatment included a total of 6 courses of chemotherapy.

The control group received bladder-preserving comprehensive treatment (transurethral bladder tumor resection + internal iliac artery infusion chemotherapy + intravesical infusion chemotherapy):

(1) Transurethral resection of bladder tumor: the patient was placed in the lithotomy position and intubated under general anesthesia. Microscopically, the depth of resection was based on the complete resection of the tumor. According to the patient's condition, the deep muscle layer and bladder could be incised accordingly. The incision was made 1 cm from the tumor boundary, followed by electrocoagulation.

(2) Internal iliac artery infusion chemotherapy: the patient's right femoral artery was cannulat-

ed. The abdominal aorta bifurcation was inserted with a multi-sided catheter with 5 mg tropisetron (Ruiyang Pharmaceutical Co., Ltd., SFDA Approval No. H20060460) and dexamethasone (Shanghai Andu Pharmaceutical Co., Ltd., SFDA Approval No. H20073181). Injection was performed on the internal iliac artery and the suppository side equally, containing 40 mg/m^2 pirarubicin (Shenzhen Wanle Pharmaceutical Co., Ltd., SFDA Approval No. H10930105), 30 mg/m^2 hydroxycamptothecin (Shanxi Zhendong Taisheng Pharmaceutical Co., Ltd., SFDA Approval No. H20063022), and 1.0 g/m^2 5-Fluorouracil (Wuhu Simcere Chinese Pharmaceutical Co., Ltd., SFDA Approval No. H20030345). Non-permanent embolization with gelatin sponge debris was performed on the distal end of the bladder artery of the affected side accordingly. The treatment was carried out once per week, and the frequency was changed to once per month after 3 months of treatment, for a total of 12 months.

(3) Intravesical infusion chemotherapy: 50 mg of epirubicin hydrochloride (Hisun Pfizer Pharmaceutical Co., Ltd., SFDA Approval No. H20030260) was dissolved in 50 mL of distilled water for bladder perfusion. After perfusion, the position of the patient was changed every 5 minutes and maintained for 30 minutes. The treatment was once per week. Two months later, the frequency was changed to 1 time/month, with a total period of 12 months.

Outcome measures

Primary outcome measures included indicators relevant to study objectives and accurately reflect treatment efficacy. Other indicators related to the purpose of the study were regarded as secondary outcome measures.

Primary outcome measures: (1) General information: The baseline information of patients was obtained through the in-hospital electronic medical record system, including the number of hospitalizations, name, gender, age, average body weight, body mass index (BMI), number of tumors, pathological grade, pathological type, residence, monthly income, living habits, and educational level.

(2) Short-term efficiency: According to the WHO 2000 Response Evaluation Criteria in Solid Tumors (RECIST criteria) [13], the patient's condition was divided into complete response (CR, the lesion has completely disappeared for over 1 month, with no emergence of new lesions and normal levels of tumor markers), partial response (PR, the sum of the maximum diameter of the target lesion was reduced by >30%, and the improvement was maintained for more than 1 month), stable disease (SD, the sum of the maximum diameter of the target lesion was reduced by <30% or increased by <20%), and progressive disease (PD, the maximum diameter of the target lesion was increased by 20% or more, or new lesions emerged). CR + PR is the objective response rate (ORR), and CR + PR + SD is the disease control rate (DCR).

(3) Incidence of adverse reactions: Data on adverse reactions of patients were obtained by medical staff through treatment detection. Adverse reactions, including leukopenia, anemia, thrombocytopenia, fever, nausea and vomiting, elevated transaminase, and elevated creatinine were recorded. The number of patients with adverse reactions was counted.

(4) Long-term treatment indicators: according to the follow-up records, the two groups of patients were followed up for 5 years. The number of patients with recurrence, metastasis, and hydronephrosis was counted.

(5) Survival: According to the follow-up records, patients in both groups were followed up for 5 years. The 3- and 5-year survival rates were counted.

Secondary outcome measures: (1) Surgical indicators: The operation time, intraoperative blood loss, gastrointestinal recovery time, and hospital stay were compared between the two groups.

(2) Quality of life: The Quality of Life Questionnaire-Core 30 (QOL-C30) scale was used to evaluate the quality of life of patients from the dimensions of emotional function, physical function, social function, cognitive function, and role function during the 5-year follow-up. The sensitivity of this scale has been confirmed by influential literature. The higher the score, the better the quality of life of the patient [14].

Table 2. Comparison of overall efficacy [n (%)]

Groups	CR	PR	SD	PD	ORR	DCR
Experimental group	18 (30.0)	24 (40.0)	10 (16.7)	8 (13.3)	42 (70.0)	52 (86.7)
Control group	12 (20.0)	24 (40.0)	12 (20.0)	12 (20.0)	36 (60.0)	48 (80.0)
χ^2	1.600	0.000	0.223	0.960	1.319	0.960
P	0.206	1.000	0.637	0.327	0.251	0.327

Table 3. Comparison of the incidence of adverse reactions between the experimental and control group [n (%)]

Indexes	Experimental group	Control group	χ^2	P
Leukopenia	36 (60.0)	42 (70.0)	1.319	0.251
Anemia	30 (50.0)	46 (76.7)	2.754	0.002
Thrombocytopenia	24 (40.0)	30 (50.0)	1.212	0.271
Fever	6 (10.0)	18 (30.0)	2.747	0.003
Nausea and vomiting	12 (20.0)	15 (25.0)	0.430	0.512
Elevated transaminase	18 (30.0)	18 (30.0)	0.000	1.000
Elevated creatinine	12 (20.0)	10 (16.7)	0.223	0.637

Statistical analysis

All data were analyzed by SPSS 20.0. GraphPad Prism 7 (GraphPad Software, San Diego, USA) was used for rendering graphics. The count data and measurement data were examined using the Chi-square test and t-test, respectively. K-M was used for survival analysis. P<0.05 was considered statistically significant.

Results

Comparison of general information

There was no statistical difference in general information between the two groups (P>0.05), as shown in **Table 1**.

Comparison of short-term efficiency

The ORR and DCR were not statistically different between the two groups (P>0.05), as shown in **Table 2**.

Comparison of the incidence of adverse reactions

The total complication incidence of the two groups of patients was statistically different (P<0.05). Both groups of patients had varying degrees of hematological toxicity and non-hematological toxicity, but no severe systemic organ toxicity. The number of cases with leukopenia, anemia, thrombocytopenia, fever, nausea and vomiting, elevated transaminase, and elevated creatinine in the experimental group was 36 (60.0%), 30 (50.0%), 24 (40.0%), 6 (10.0%), 12 (20.0%), 18 (30.0%), and 12 (20.0%), respectively. Those in the control group were 42 (70.0%), 46 (76.7%), 30 (50.0%), 18 (30.0%), 15 (25.0%), 18 (30.0%), and 10 (16.7%), respectively. The number of patients with anemia and fever in the experimental group was significantly lower than that in the control group (P<0.05), as shown in **Table 3**.

Comparison of long-term treatment indicators

In the experimental group, there were 8 cases of recurrence, 8 cases of metastasis, and 12 cases of hydronephrosis. The control group, 18 cases had recurrence, 17 cases had metastasis, and 6 cases had hydronephrosis. The incidences of recurrence, metastasis and hydronephrosis in the experimental group were significantly lower than those in the control group (all P<0.05), as shown in **Figure 1**.

Comparison of survival

The 3-year survival rate was not statistically different between the experimental group and the control group (86.7% *vs* 75.0%, P>0.05). The 5-year survival rate of the experimental group was significantly higher than that in the control group (70.0% *vs* 51.7%, P<0.05), as shown in **Figures 2** and **3**.

Comparison of surgical indicators

The surgical indicators in the experimental group were significantly better than those in the control group (P<0.001), as shown in **Table 4**.

Comparison of quality of life

The 5-year follow-up revealed no significant difference in the quality of life scores between the two groups (P>0.05), as shown in **Table 5**.

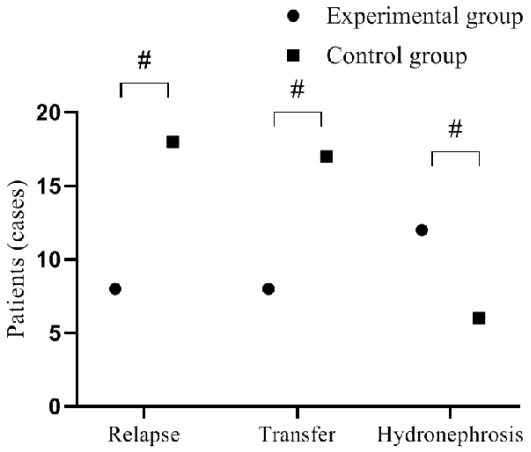

Figure 1. Comparison of long-term treatment indicators. Note: the horizontal axis represents relapse, metastasis, and hydronephrosis from left to right, and the vertical axis represents the number of patients (cases); the dots in the figure represent the experimental group, and the squares represent the control group; # represents P<0.05.

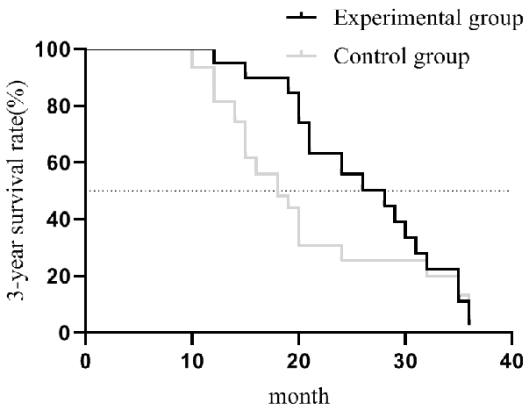

Figure 2. Comparison of 3-year survival rate [n (%)]. Note: the horizontal axis represents time (month), and the vertical axis is the 3-year survival rate (%); the black line in the figure represents the experimental group, and the gray line represents the control group.

Discussion

Currently, the standard treatment for invasive bladder cancer is radical cystectomy with pelvic lymph node dissection and urethral modification, which has promising clinical efficacy. The large surgical trauma and the high postoperative complication incidence compromise the quality of life of patients. This underlines the importance of the exploration of new treatment methods for invasive bladder cancer [14-16], to

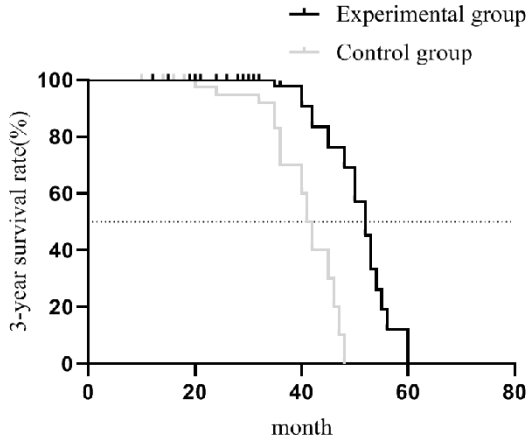

Figure 3. Comparison of 5-year survival rate [n (%)]. Note: the horizontal axis represents time (month), and the vertical axis is the 5-year survival rate (%); the black line in the figure represents the experimental group, and the gray line represents the control group.

preserve the bladder and ensure efficiency. This study found that compared with those who received radical cystectomy, patients with invasive bladder cancer who were treated by cystopexy + intravesical infusion chemotherapy + intravenous chemotherapy showed no significant decrease in the survival rate. This method requires preoperative assessment of tumor properties and depth of infiltration, supplemented by effective chemotherapy regimens and close postoperative follow-up [17-19]. The GC chemotherapy regimen has excellent efficacy and high safety. The efficiency rate exceeded 70% and reported CR up to 20%. This is widely used in neoadjuvant treatment of advanced and locally advanced bladder cancer [20, 21]. This treatment is indicated for patients with intermediate bladder cancer, which can increase the long-term survival rate of patients to 60% and improve the prognosis [22]. After bladder cancer surgery, bladder infusion chemotherapy drugs can effectively reduce the recurrence rate of bladder cancer and prevent tumor progression. Pirarubicin is an anthracycline antitumor drug that kills tumor cells in the S phase by inhibiting DNA replication and transcription by embedding DNA double strands and/or inhibiting DNA polymerase, terminating the tumor cell cycle. Compared with adriamycin and epiamycin that are used in the early clinical stage, pirarubicin has stronger antitumor effects. Pirarubicin has been shown to prevent

Table 4. Comparison of surgical indicators ($\bar{x}$±s)

	Experimental group (n=60)	Control group (n=60)	t	P
Operation time (min)	42.65±3.65	268.21±12.21	137.100	<0.001
Intraoperative blood loss (mL)	62.68±23.68	365.12±23.68	69.955	<0.001
Gastrointestinal recovery time (d)	2.00±0.68	2.64±0.54	5.709	<0.001
Hospitalization stay (d)	12.68±2.41	18.54±2.23	13.824	<0.001

Table 5. Comparison of quality of life ($\bar{x}$±s, point)

	Experimental group (n=60)	Control group (n=60)	t	P
Emotional function	43.65±2.15	44.11±2.68	1.037	0.302
Physical function	60.23±3.54	60.58±3.20	0.568	0.571
Social function	49.12±3.23	50.11±3.54	1.600	0.112
Role function	50.65±2.68	51.23±2.01	11.341	0.183
Cognitive function	55.68±2.56	55.98±2.41	0.661	0.510

local recurrence of bladder cancer to some extent. As none of the three major guidelines recommend monotherapy with local cystectomy, chemotherapy, or radiotherapy, some patients may undergo radical cystectomy based on the GC regimen to increase the 5-year survival.

With the increasing demand for improving quality of life of cancer patients, the comprehensive treatment of bladder preservation has achieved a certain range of clinical applications. It has been reported that with comparable efficacy to radical cystectomy, this treatment optimizes perioperative indicators and ensures the postoperative quality of life of patients. V Grajales et al. reported that the 3- and 5-year survival rates of patients undergoing transurethral bladder tumor resection were 53.3% and 40.1%, respectively. Those patients undergoing radical cystectomy were 52.1%, and 41.0%, with no statistical difference between the two methods [23]. It has also been shown that patients who underwent radical cystectomy have better long-term outcomes compared to those receiving transurethral resection of bladder tumors, with a significantly lower probability of postoperative recurrence and metastasis and a 5-year survival rate exceeding 50%. To date the consensus upon its long-term efficacy has yet been developed in the academic community [24]. This study found that the ORR and DCR of the experimental group were not statistically different from those of the control group. The incidence rates of recurrence and metastasis in the experimental group were significantly lower. The comparison of patient survival revealed no significant difference in the 3-year survival rate between the two groups and a significantly higher 5-year survival rate in the experimental group (P<0.05). This indicated no significant difference in the short-term efficacy, but an evident difference in the long-term efficacy. The GC chemotherapy regimen was administered to patients in the experimental group with radical cystectomy. This successfully achieved control of local and distant micro-metastases. The experimental group outperformed the control group in terms of postoperative survival. After 5 years of follow-up, patients were assessed for their quality of life. The results revealed no significant difference in the long-term quality of life between the two groups. This suggested that the comprehensive treatment of bladder preservation may not affect the long-term quality of life of patients with bladder cancer.

After chemotherapy, the two groups of patients had varying degrees of hematological toxicity and non-hematological toxicity, but no severe systemic organ toxicity. The number of patients with anemia and fever in the experimental group was significantly lower than that in the control group, indicating that the two treatments had a similar safety profile. There are many factors that affect the prognosis of patients with muscle-invasive bladder cancer. The treatment method of radical cystectomy combined with GC chemotherapy used in the experimental group still lacks large-scale controlled studies. The application effects of the combination therapy need to be explored in more depth. The limitations of this study also lie in the absence of multifactorial analysis and exploration of risk factors affecting prognosis to give patients targeted interventions, which will be studied in the future to obtain more clinical information.

Conclusion

In summary, with favorable long-term efficacy, radical cystectomy combined with GC chemotherapy for the treatment of invasive bladder cancer has a low probability of adverse reactions and is beneficial to increase the 5-year survival rate of patients.

Disclosure of conflict of interest

None.

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