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Clinical efficacy of hyperthermic intraperitoneal chemotherapy on the malignant ascites in gastric cancer patients following the preoperative radiotherapy

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► ***Original article***

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ABSTRACT

***Background*:** To investigate the clinical efficacy of hyperthermic intraperitoneal chemotherapy in combination with the malignant ascites in gastric cancer following the Intensive preoperative radiotherapy for radical surgery of tumor. ***Materials and Methods*:** We selected a total of 112 gastric cancer patients who had been operated on for radical surgery of tumor in this hospital as subjects that were randomized into the control group and the observation group, with 56 patients in each group. Patients in the control group took the abdominal aspiration in combination with the intravenous chemotherapy, while those in the observation group underwent the hyperthermic intraperitoneal chemotherapy. After treatment, we compared the effectiveness rate, levels of tumor markers, incidence rates of adverse reactions, and Karnofsky (KPS) scores between the two groups. ***Results*:** In the observation group and the control group, the effectiveness rates of patients were 71.43% and 44.64%, showing the statistical significance of the difference ($P < 0.05$); after treatment, the levels of CEA, CA125, and CA199, tumor markers, were decreased compared to before treatment ($P < 0.05$). The incidence rates of adverse reactions were 75.00% and 82.14%, showing no statistical significance of difference ($P > 0.05$). Following the treatment, the KPS scores were improved in two groups compared to before treatment ($P < 0.05$). ***Conclusion*:** For gastric cancer patients with malignant ascites, hyperthermic intraperitoneal chemotherapy excels in the clinical efficacy by decreasing the level of tumor markers, to improve the life quality of patients, but with no increase in the incidence rate of adverse reactions.

INTRODUCTION

Gastric cancer, as a common malignant disease with a high prevalence and mortality rate, has ranked at 4th in the prevalence and 2nd in the mortality rate of all cancers in the world, severely threatening the health and life of human beings [(1)]. Amongst the patients, 36% of them have progressed into the advanced stage at the diagnosis, 22% of which report peritoneal metastasis [(2)]. Currently, gastric cancer patients mainly take chemotherapy, radiotherapy, surgical treatment, and medication, in which patients in advanced stage respond well to the chemotherapy, with obvious mitigation of clinical symptoms, improvement in survival duration, and the life quality of patients [(3)]. High-fat, high-salt, high-nitrate diet, history of Helicobacter pylori infection, EBV virus, genetic factors (involvement of P53, COX2 genes), precancerous gastric lesions, and tobacco use are all risk factors [(4)]. Weight loss and loss of food intake due to appetite and premature satiety are common symptoms of the disease. In addition to host risk factors, tumor characteristics including primary tumor size, lymph node invasion, and distant metastasis play a role in prognosis [(5-6)].

However, gastric cancer patients in the advanced stage manifest with the malignant ascites referring with the abnormal increase in the intraperitoneal fluid due to the extensive peritoneal metastasis, the massive loss in protein, renal function disorders that increase the difficulty of treatment [(7-8)]. According to the available data, gastric cancer patients with malignant ascites usually have a survival duration of 12 to 19 weeks, severely affecting the life quality of

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patients. Thus, an effective strategy is very important for gastric cancer patients with malignant ascites [9]. The choice of treatment is based on the stage of the disease and surgery is the basis of the definitive treatment in the early stages. Nowadays, chemotherapy treatments and sometimes radiotherapy is used in the form of neoadjuvant and also adjuvant in certain stages of the disease. Various researches have been done in the Cancer Surgery Center regarding the type of treatment regimen and drugs used and also the timing of chemotherapy [10-11]. Hyperthermic intraperitoneal chemotherapy is an advanced method of chemotherapy fluid delivery to the body, ensuring that the drug would be available to all of the interest areas after the surgery. This method was developed in 2015 by Lotti *et al.* and after the gastric cancer surgery of a patient ended, it was performed laparoscopically, known as Intraperitoneal hyperthermic chemoperfusion (HIPEC), and the result was an improvement in providing a suitable temperature and better circulation of chemotherapy fluid. This method especially prevents surgical adhesions that could impede the complete circulation of the drug [12].

Shchepotin *et al.* combined Intensive preoperative radiotherapy with HIPEC in gastric carcinoma [13]. The meta-analysis of Guo *et al.* showed that Gastric cancer treated with preoperative radiotherapy was more efficient than surgery alone [14]. In recent years, many studies have focused on high-quality radiotherapy to gastric tumors, along with the surgical requirements to ensure the delivery of high-quality surgery. Some trials have been evaluated the function of preoperative radiotherapy in conjunction with surgery; while still there is not any indenture available now [15].

The current study aims to use a novel treatment regimen for preoperative care of gastric cancer. This strategy is designed based on intensive preoperative radiotherapy (20 Gy in 4*5 Gy fractions [13]) and also HIPEC delivery after the surgery. We also evaluated Karnofsky's daily function status along with biological markers in serum. These variables were not evaluated before this and could help the interpretation of final survival results.

MATERIALS AND METHODS

This was a randomized trial performed between January 2018 and January (Registration number: 2018 NO.23) in a total of 112 gastric cancer patients who had been operated on for radical surgery of tumor and after a while was experiencing malignant ascites. Inclusion criteria were patients with malignant ascites in volume > 3000 mL indicated by ultrasonic sound B; patients with normal results in echocardiogram, routine examinations of blood and urine, and functional test of liver and kidney; patients with KPS > 60; patients with an expected survival duration > 3 months; patients with intraperitoneal diffusive metastasis of tumors confirmed by MRI and CT. Patients with coagulative dysfunction, extensive celiac adhesion, or intestinal obstruction were excluded from this study. This study had been reviewed and approved by the Ethical Committee of Zhengzhou hospital, and all patients agreed to participate in the study voluntarily after they were informed of the content of the study. These patients were included in this study if had received intensive preoperative external beam radiation therapy. Blinding of researchers was not possible in this study. Patient's demographic data and Eastern Cooperative Oncology Group performance status (ECOG-PS) was recorded. 5 cc of blood was taken to measure tumor markers at the beginning of the study, after accession of informed consent. Tumor markers, including CEA, CA125, and CA199, were evaluated at 7 d prior to the treatment and 28 d after treatment. Then patients were scheduled for following treatment groups:

Irradiation, radiation therapy was delivered each day for four days through opposite anterior-posterior fields. The dose of radiotherapy was 5 Gy, for a total of 20 Gy doses. Cobalt-60 Machine (No: 1966.0043; Atomic Energy of Canada Ltd, Canada) was used for radiations. Then the surgery was performed for all patients in both groups.

Control group, patients in the control group took the abdominal aspiration in combination with intravenous chemotherapy. Chemotherapy regimens were selected according to the practical condition of patients, they underwent a total of 3 to 8 courses of chemotherapy and the aspiration at the first volume of 1000 mL, followed by 500 mL/d.

HIPEC group, those in the Case or observation group underwent hyperthermic intraperitoneal chemotherapy. In brief, patients received three time's hyperthermic intraperitoneal chemotherapy, and 3 to 8 courses of intravenous chemotherapy, in which the chemotherapy regimens were chosen based on the primary condition. Dose for chemotherapeutics in hyperthermic intraperitoneal chemotherapy was maintained consistent with that of the intravenous chemotherapy. Under the guidance of laparoscope, four channels were established specifically for hyperthermic intraperitoneal chemotherapy to connect the treatment apparatus. Hyperthermic perfusion was performed by the mixture of chemotherapeutics and normal saline in the volume of 4000 to 6000 mL at a rate of 450 to 600 mL/h at 43°C.

Outcome measurement and follow-ups

According to the criteria for evaluation of ascites stipulated by the World Health Organization (WHO) [16-17], efficacy was divided into 4 grades: Complete remission (CR): no ascites inside the abdomen for

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consecutive 28 d or longer; partial remission (PR): decrease in volume of ascites by more than 50% for consecutive 28 d or longer; stable disease (SD): decrease or no increase in the volume of ascites by less than 50%; progressive disease (PD): increase in the volume of ascites. The percentage of the total number of CR and PR to the total patients was taken as the remission rate (RR). Efficacy was evaluated 28 days later in clinical visit follow-up. Patient's blood biomarkers were evaluated in 28th day.

5 cc of blood to measure tumor markers of CEA, CA125, and CA19 were taken from the patient and sent to the relevant laboratory. Blood samples were immediately centrifuged in the laboratory and serum samples were frozen and stored for laboratory analysis. Tumor markers were measured under the supervision of a laboratory technician by the ELISA method using CanAg kits (Product number 401-10, Japan). CEA<5 g/ml and CA19-9 and CA125 <25u/ml were considered normal.

The incidence of adverse reactions was also evaluated. After treatment, we observed and evaluated the adverse reactions, including leukopenia, decrease in hemoglobin, thrombocytopenia, gastrointestinal reaction, liver function damage, and renal function damage.

KPS score for assessing the life quality of patients was evaluated before and after treatment by use of the KPS method (from 0 to 100 points), and a higher score represents the better life quality.

Statistical analysis

Data in this study were processed and analyzed using the SPSS 20.0 software. Measurement data in normal distribution were expressed in form of mean ± standard deviation, while the count data in form of n (%). Intergroup comparison was carried out by use of t test and chi-square test. α=0.05 was set as the inspection level, while $P < 0.05$ suggested that the difference had statistical significance.

RESULTS

Patients were randomized into the control group and the observation group, with 56 patients in each group. In the control group, there were 25 males and 31 females, aged from 29 to 80 years, with an average of (49.12±4.24) years; in the observation group, patients aged from 30 to 78 years, with an average of (48.52±3.41) years. There were no difference in the Eastern Cooperative Oncology Group performance status (ECOG-PS) of patients in two groups. Comparison of the general data of patients, including sex and age, showed that differences had no statistical significance ($P > 0.05$), indicative of the comparability of data (table 1).

Table 1. Demographic data of two groups [n (%)].

Group		Observation group	Control group	P
Sex, male, n (%)		27(48.21)	25(44.64)	0.641
Age, Year, Mean±SD		48.52±3.41	49.12±4.24	0.181
ECOG-PS	1	14(25)	12(21.43)	0.487
	2	23(41.07)	28(50)	
	3	11(19.64)	10(17.86)	
	More than 3	8(14.29)	6(10.71)	

Comparison of the effectiveness rate between two groups showed that in the observation group and the control group, the effectiveness rates of patients were 71.43% and 44.64%, respectively, showing significance statistical difference ($P < 0.05$; table 2). CEA levels decreased from 28.23±7.35 ng/mL to 14.11±6.92 ng/mL Observation group, having a similar amount of decrease in control group; while final CEA levels at 28th day was significantly lower in Observation group (P=0.023). CA125 levels decreased from 70.82±18.72 U/mL to 33.78±13.28 U/mL Observation group. Also, in control group CA125 levels decreased; while final CA125 levels at 28th day was significantly lower in Observation group (P=0.041). CA199 levels decreased in both groups (54.63±15.51 to 28.92±12.64 U/mL in Observation group vs. 53.86±16.23 to 29.46±11.95 U/mL in control). Final CA199 levels at 28th day was significantly lower in Observation group (P=0.0.012).

Table 2. Comparison of the effectiveness rates and biomarkers between two groups.

Group		Observation group	Control group	P
N		56	56	-
complete remission		21(37.50)	9(16.07)	0.001
partial remission		19(33.93)	16(28.57)	
stable disease		9(16.07)	14(25.00)	
partial disease		7(12.50)	17(30.36)	
Effectiveness rate (%)		40(71.43)[a]	15(44.64)	
CEA (ng/mL), Mean±SD	Before treatment	28.23±7.35	28.15±7.81	0.564
	After treatment	14.11±6.92[a]	13.50±6.73[a]	0.023
CA125 (U/mL), Mean±SD	Before treatment	70.82±18.72	71.34±18.41	0.742
	After treatment	33.78±13.28[a]	34.27±12.78[a]	0.041
CA199 (U/mL), Mean±SD	Before treatment	54.63±15.51	53.86±16.23	0.317
	After treatment	28.92±12.64[a]	29.46±11.95[a]	0.012

Comparison of the incidence rates of adverse reactions between two groups showed that the incidence rates of adverse reactions were 75.00% and 82.14%, showing no statistical significance of difference ($P > 0.05$; table 3). Comparison of KPS scores between two groups revealed that following the treatment, the KPS scores were improved in two groups when comparing to the levels before treatment, while the scores in the observation group were higher than those in the control group ($P < 0.05$; table 3).

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Table 3. Comparison of the incidence rates of adverse reactions and KPS scores between two groups.

Group		Observation group	Control group	P
Leukopenia, n		9	9	0.001
Decrease in hemoglobin, n		9	10	
Thrombocytopenia, n		9	10	
Gastrointestinal reaction, n		10	10	
Liver function damage, n		5	7	
Incidence rates of adverse reactions		42(75.00)	46(82.14)	
KPS scores	Before treatment	53.80±8.65	54.34±8.92	0.7
	After treatment	79.47±7.27[ab]	64.74±8.48[a]	0.003

Note: a P < 0.05 vs. the level before treatment in the same group; b P < 0.05 vs. the control group

DISCUSSION

Gastric cancer associated malignant ascites has a poor prognosis with a median survival of less than one year [18]. Since recurrent gastric cancer remains confined to the abdominal cavity in many patients, regional therapies like hyperthermic intraperitoneal chemotherapy (HIPEC) have been investigated for GC [19-22]. HIPEC is an adjuvant therapy after a curative surgery, HIPEC has been shown to improve survival and reduce peritoneal recurrences in many randomised trials in Asian countries as a definitive treatment in GC, HIPEC is the only therapeutic modality that has resulted in long-term survival in select groups of patients; as a palliative treatment in advanced GC with intractable ascites, HIPEC has been shown to control ascites and reduce the need for frequent paracentesis [23].

Radiation therapy produced a tendency toward improved survival at 3 and 5 years in patients with well differentiated tumors as compared with surgery alone consisting of 22% at 3 years and 9.2% at 5 years [24]. Preoperative intensive radiation therapy without hyperthermia did not significantly improve 3 - or 5-year survival in comparison with surgery alone. The cumulative benefit of radiation and hyperthermia when compared to surgery alone improved survival by 22.1% at 3-years [25].

Facchiano *et al.* treated five patients with malignant ascites after palliative resection of gastric cancer by laparoscope-assisted HIPEC in a hospital affiliated to the Paris University. The results showed that the operation went on smoothly without related complications for a mean 181 min; malignant ascites were eliminated in all 5 cases. Facchiano suggests that laparoscope-assisted HIPEC in patients with malignant ascites after palliative resection of gastric cancer is safe and feasible, with robust clinical effect [26].

Ba *et al.* have successfully developed a High Precision Intraperitoneal Hyperthermic Perfusion Treatment system with independent intellectual property rights. Bloody ascites in two cases and chyle -like malignant ascites in one case turned clear very quickly after the first laparoscope-assisted HIPEC [27]. The median survival time was 5 month, which is prolonged as compared with the traditional therapy. General status, mental status, appetite and body weight improved, symptoms of anemia were alleviated, and initial clinical efficacy was satisfactory in the patients [28]. All these results imply that laparoscope-assisted HIPEC has good clinical efficacy.

CONCLUSION

Finally, we can conclude that in patients with gastric cancer who manifest with malignant ascites, hyperthermic intraperitoneal chemotherapy outperforms chemotherapy and surgery method in terms of therapeutic effectiveness, lowering tumor markers and improving patient quality of life while reducing the risk of adverse reactions.

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***Conflicts of interest*:** *Declared none.*

***Ethical considerations*:** This research was approved by the institutional Ethical Committee with registration number: 2018 NO.23

***Author contributions*:** Z. Wang,P. Wang, L. Lv,Y. Liu and C.J. Sun contributed to the conception of the study; P. Wang, L. Lv and C.J. Sun performed the experiment; Y. Liu contributed significantly to analysis and manuscript preparation; Z. Wang,P. Wang and C.J. Sun performed the data analyses and wrote the manuscript; L. Lv helped perform the analysis with constructive discussions.

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