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ORIGINAL ARTICLE

Hyperthermic intraperitoneal chemotherapy plus high-frequency diathermic therapy followed by intravenous chemotherapy versus intravenous chemotherapy alone for postoperative adjuvant treatment of gastrointestinal cancer: a comparative research study

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Summary

Purpose: *To evaluate the therapeutic efficacy and toxicity of hyperthermic intraperitoneal chemotherapy (HIPEC) plus high-frequency diathermic therapy (HFDT) followed by intravenous chemotherapy vs intravenous chemotherapy alone for adjuvant treatment of postoperative gastrointestinal neoplasms.*

Methods: *Fifty-two gastrointestinal carcinoma patients who were radically operated were enrolled and divided into the treatment group and the control group. In the treatment group, 25 patients were treated with combination of HIPEC+HFDT and subsequent intravenous chemotherapy, while in the control group 27 patients received intravenous chemotherapy alone. Post-therapeutic complications and adverse reactions, time to progression (TTP) and overall survival (OS) were compared between these two groups.*

Results: *Difference in toxic reactions between the two groups was not statistically significant (p>0.05). Postoperative progression-free survival (PFS) rate at 12 and 40 months after radical surgery was 72.0 and 54.0% respectively in the treatment group, and 65.8 and 11.5% respectively in the control group (p=0.108). TTP was statistically significantly longer in the treatment group than in the control group (median TTP 40.1 vs 18.5 months, p=0.027). Postoperative OS at 12 and 20 months after radical surgery was 88.0 and 78.0% respectively in the treatment group and 92.6 and 72.7% in the control group, without significant difference.*

Conclusion: *After radical surgery, combination of HIPEC+HFDT and subsequent intravenous chemotherapy brings about superior PFS compared with intravenous adjuvant chemotherapy alone, while having no more complications and adverse reactions.*

Key words: *adjuvant treatment, gastrointestinal neoplasms, high-frequency diathermic therapy, hyperthermic intraperitoneal chemotherapy*

Introduction

Implanting and metastasis of tumors in the abdominal and pelvic cavity is the main cause of treatment failure for gastrointestinal malignancies. According to literature, in cases of postoperative recurrence of gastric or colorectal cancer, the incidence of peritoneal metastasis can be as high as 50% [1,2]. Despite radical surgery and systemic chemotherapy, the majority of patients with

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tumors are prone to develop peritoneal metastasis or tumor progression, and the long-term therapeutic efficacy is low due to the existence of small residual lesions and intraperitoneally falling off or iatrogenic implanting of free cancer cells, as well as the plasma-peritoneal shielding effect on systemic chemotherapy. Therefore, to improve the therapeutic efficacy, it is important to effectively wipe out free cancer cells and minimal residual lesions in the abdominal cavity [3]. Since the 1980s, HIPEC theory has been proposed, animal and cell models have been established [4,5], and this therapy has been applied to prevent the peritoneal metastasis of gastrointestinal neoplasms (GIN) in clinical trials [6,7]. With the combination of local chemotherapy, diathermia and a large volume mechanical lavage, this therapy is expected to maximize the removal of abdominal tumor cells and reduce the probability of tumor metastasis, thus, prolonging the survival of patients. For more than 30 years, research institutions have reported a lot of HIPEC practices, forming a treatment model for locally advanced GIN patients: a radical surgery or optimal cytoreductive surgery plus HIPEC [8]. However, due to the impact of HIPEC on long-term survival in patients and the controversy on the safety and practical significance of diathermia, HIPEC has not become an internationally recognized guideline vs standard treatments of GINs [9]. Therefore, it is necessary to thoroughly study this disputed problem and continue to carry out clinical researches.

The purpose of this study was to explore whether HIPEC is possibly more efficient in improving the overall efficacy, especially in reducing the postoperative recurrence rate of GINs and in improving the prognosis of these patients.

Methods

Clinical material

Fifty-two GIN patients subjected to radical surgery from April 2005 to April 2010 and pathologically diagnosed after their operation were enrolled and divided into two groups: the treatment group and the control group. The treatment group consisted of 25 patients including 15 males and 10 females with age ranging from 34 to 78 years (median 55). This group included 16 colorectal cancer and 9 gastric cancer patients. The control group consisted of 27 patients, including 14 males and 13 females with age ranging from 35 to 80 years (median 60). This group included 16 colorectal cancer and 11 gastric cancer patients. Patients in the treatment group received HIPEC+HFDT followed by intravenous chemotherapy, and patients in the control group received intravenous chemotherapy alone. The therapeutic efficacy of these two groups was analyzed by retrospective cohort analysis.

Therapeutic methods

Prior to HIPEC all patients were subjected to radical operations with R0/R1 resections.

The treatment group consisted of 25 patients. Among them, 24 patients were subjected to ascites drainage and HIPEC guided by color Doppler ultrasound. All procedures were performed when the surgical wounds had healed, 5-53 days after radical surgery (3 patients within 2 weeks after surgery, 11 patients within 2-3 weeks after surgery, 6 patients within 3-4 weeks after surgery, and 4 patients within 4-8 weeks after surgery, and 1 patient before neoadjuvant chemotherapy and within 20 days of radical surgery), and all patients were fit to receive chemotherapy. Cisplatin plus 5-FU (EP) treatment was adopted as the chemotherapy regimen: 100 mg/m^2 of cisplatin+3 g/m^2 of 5-FU. The total dosage was divided into 3 administrations which were intraperitoneally perfused on the first, fifth and ninth day with a course repetition in 21 days.

HIPEC

HIPEC started with intraperitoneal injection of 1,000 ml of normal saline. Then the chemotherapeutic drugs were dissolved in 500 ml of normal saline, heated by a thermal cycling perfusion machine to 45°C, and perfused into the abdominal cavity through an abdominal indwelling tube with a circulation perfusion apparatus. At the same time, the following drugs were intraperitoneally injected: 10 mg of dexamethasone to prevent allergy and abdominal adhesions, 160 mg of gentamicin sulfate to prevent infection, 20 ml of lidocaine chloride for pain relief, and 200 million U of interleukin-II to enhance chemotherapy efficacy. Before and after chemotherapy, conventional antiemetic therapy, liver protection through glutathione intravenous infusion, hydration with saline to ensure enough urine output, alkalization and diuretic therapy were administered to reduce side effects.

Each perfusion of chemotherapy was immediately followed by HFDT. Diathermic treatment methods was as follows: a non-intrusive *in vitro* diathermia machine HG-2000 (Hokai Medical Equipment, Guangdong, China) was used. The patients were asked to lay on the treatment bed in supine position, a circular electrode plate was placed above and below the level of abdominal perfusion at a distance of 5 cm from the skin. When the system of the machine started, output voltage was set between 180-200 V, output power was set between 60-70%, working frequency was set at 13.56 MHz, and the temperature was set between 41.5-42.5°C. The duration of each treatment was 60 min. Patients in the treatment group received systemic intravenous chemotherapy after the end of the perfusion treatment. The

chemotherapy regimen recommended by the National Cancer Comprehensive Treatment Network (NCCN) was adopted: colorectal cancer using the FOLFOX regimen, and gastric carcinoma using docetaxel+cisplatin+5-FU or cisplatin+S-1. In the control group, 27 patients were treated with systemic intravenous chemotherapy within 0.5-1 month of radical surgery, or before and after radical surgery. The intravenous chemotherapy regimen for this group was the same as that in the treatment group.

Statistics

The statistical software SAS 8.1 was used to analyze and process the data. Counting data of the two groups were evaluated using Fisher's exact test and rank-sum test. Survival analysis was performed using the Kaplan-Meier method with log-rank test for therapeutic efficacy assessment. P values less than 0.05 were considered statistically significant.

Results

All patients in the two groups had adenocarcinoma. Differences in gender, age, primary tumor location, type and grade of tumor differentiation, stage and follow-up between the two groups were not statistically significant (Table 1).

Comparison of adverse reactions and complications between the two groups

Adverse reactions in patients were evaluated based on the WHO standards and classified according to the maximum adverse reactions that occurred in the course of treatment. Adverse reactions and complications between the two groups are listed in Table 2. Statistical analysis revealed that the differences in adverse reactions and complications between the two groups were not statistically significant.

Comparison of therapeutic efficacy between the two groups
Disease-free survival analysis

Up to June 15,2011, tumor progression occurred in 36% of the patients in the treatment group. Point estimate of survival analysis revealed the following: PFS rate was 72% at one year after surgery and 54.0% at 40 months after surgery. Median TTP was 40.1 months with 95% confidence interval (95% CI) from 10.5 months to the upper value that is not reached. In the control group, tumor progression occurred in 67% of the patients, while PFS rate was 65.8% at one year after surgery, 34.6% at 2 years after surgery, 23.1% at 3 years after surgery, and 11.5% at 40 months after surgery. The median TTP in the control group was 18.5 months with 95% CI 12-36 months, shorter than in the treatment group (p=0.027).

Comparison of TTP between the two groups

Log-rank test revealed significant difference between the two groups. TTP was prolonged in the treatment group as compared to the control group (p=0.027). Furthermore, this suggests that after GIN radical surgery, HIPEC+HFDT and subsequent intravenous chemotherapy could significantly prolong DFS compared to intravenous chemotherapy alone (median TTP: 40.1 vs 18.5 months).

Overall survival analysis

Up to June 15, 2011, 20% of the patients in the treatment group died. One-year survival rate was 88% and 20-month survival rate was 78.0%. In this group, 13 patients survived for more than

Table 1. Patient and disease characteristics in the 2 groups

Characteristics	*IP group (N=25)*	*VD group (N=27)*	*p value*
Gender			
Male	15	14	0.59
Female	10	13	
Age (years)			
<65	17	20	0.76
≥65	8	7	
Tumor location			
Cancer of the large intestine	16	16	0.78
Cancer of the stomach	9	11	
Tumor stage			
I	1	1	
II	7	4	0.59
III	14	20	
IV	3	2	
Kind of adenocarcinoma and cell histology differentiation			
Signet ring cell carcinoma	4	1	
Poorly or moderately differentiated carcinoma	6	6	0.56
Moderately or well differentiated carcinoma	10	15	
Well differentiated carcinoma	2	1	
Not defined	3	4	
Completed follow-up (years)			
>1	25	27	0.88
>2	16	23	
>3	7	9	
>5	0	1	

IP: intraperitoneal perfusion group, VD: intravenous drip group

Table 2. Comparison of common adverse effects and complications between IP and VD groups

Groups	*Grade*	*Cases of common adverse effects*					
		Bone marrow suppression	*Digestive reactions*	*Liver function*	*Kidney function*	*Peripheral neurotoxicity*	*Other complications*
IP group (N=25)	0	6	6	16	21	21	3 cases of incomplete ileus
	I	6	9	5	4	4	
	II	9	7	3	0	0	
	III	3	3	1	0	0	
	IV	1	0	0	0	0	
VD group (N=27)	0	6	7	16	25	21	1 case of drug fever; 1 case of aplastic anemia
	I	7	8	5	2	6	
	II	10	7	5	0	0	
	III	2	5	1	0	0	
	IV	2	0	0	0	0	
Sum check/ Fisher's exact test / p value		1.00	0.94	0.92	0.41	0.73	>0.05

For abbreviations see footnote of Table 1

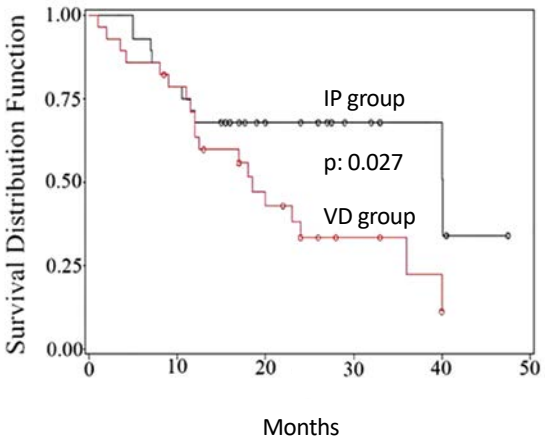

Figure 1. Time to progression of intraperitoneal (IP) and intravenous drip (VD) group, Medians: IP group, MTTP: 40.1 months; VP group, MTTP: 18.5 months.

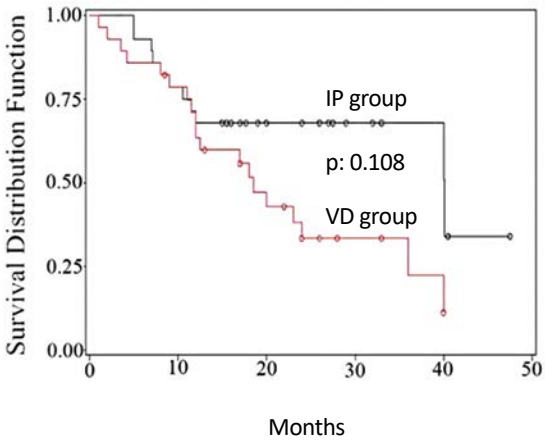

Figure 2. Overall survival of intraperitoneal perfusion (IP) and intravenous drip VD group, Medians: IP group, could not be estimated. VD group 36 months.

2 years during follow-up, and the longest survival duration was 47.5 months. However, due to the high proportion of censored data, median survival time could not be estimated. Since no death was registered among patients who had survived for more than 2 years, the long-term survival rate could not be calculated by point estimate. In the control group, 45% of the patients died. Survival rate was 92.6% at one year after surgery, 72.7% at 20 months after surgery, and 36.7% at 40 months after surgery (p=0.108).

Comparison of survival between the two groups

Log-rank test revealed that the difference in survival between the two groups was not statistically significant (p=0.108). The DFS and OS curves of the two groups drawn by the Kaplan-Meier method are shown in Figures 1 and 2.

Discussion

The common recurrence and metastasis locations after radical resection for GIN include the resection site, peritoneal surface and the liver. The prevention of tumor recurrence and metastasis in these regions is of great significance to improve prognosis. Ideal chemotherapeutic measures should provide high concentrations of anticancer drugs at the above sites, but bring about small systemic and local toxicity. HIPEC has basically met this requirement, and is a selective regional chemotherapy measure that has been designed according to anatomical characteristics

[3]. It can directly provide high concentrations of anticancer drugs in the abdominal cavity and improve local lesion cytotoxicity. At the same time, these drugs can be absorbed into the liver through blood capillaries and lymphatic vessels, and subsequently to the portal vein and can kill cancer cells in the liver [10] and reduce the toxic side effects on the whole body through hepatic detoxification. All the above-said can be summed up as the following theory: a) diathermia has a direct cytotoxic effect on tumor cells and a synergistic effect with chemotherapy [5,11-15]; b) tumor cells have poorer heat tolerability than normal cells. High temperatures can selectively kill cancer cells through various mechanisms such as activation of lysosomes, promotion of cell membrane protein denaturation, interference with DNA and RNA synthesis in cancer cells, promoting the production of tumor necrosis factor, and destruction of the inner environment which is essential for tumor tissue to survive. Synergistic mechanisms of diathermia and chemotherapy are as follows: a) through thermal kinetic effects, heating accelerates the reaction of chemotherapeutic drugs with target cancer cells, improving the reaction rate of the drugs to the target molecule and thus increasing the sensitivity to chemotherapy; b) heating can promote the crosslinking of platinum chemotherapeutic drugs with the tumor cell DNA, enhancing the lethal effect of chemotherapy drugs; c) heating can increase the permeability of cancer cells, promoting the penetration of chemotherapeutic drugs into the cells and improving their anticancer activity; d) moderate-high temperatures can inhibit the activity of the DNA repair enzymes, inhibiting the repair of cell damage after chemotherapy, thus consolidating the effect of chemotherapy.

In the 1980s and 1990s, from theory to practice, HIPEC has been gradually accepted in the clinic, and a number of institutions have begun to carry out studies on this. Many authors have reported that the application of HIPEC was quite effective in the reduction of postoperative recurrence of GIN and improvement in patient survival [16].

In the field of GIN, Chinese researchers have reported a number comparative studies on HIPEC combined with intravenous chemotherapy vs intravenous chemotherapy alone in patients with advanced GIN after an operation. In 2010, Mingshu Zhang et al. [17] reported that the 5-year survival rates of these two treatment methods in 168 elderly patients with GIN were 27.4 vs 9.7%. In 2011, Feng Zhang [18] reported that in 135 advanced GIN patients, the 5-year survival rates were 58.5 vs 41.8%, and the local recurrence rates were 14.9 vs 30.8%. In 2011, Guanghong Han et al. [19] reported that in 164 patients, the 5-year survival rates were 42.9 vs 21.3%. All differences between these two treatment methods were statistically significant. In 2013, Xiaojiang Wu et al. reported that in GIN patients with ovarian metastasis, the median survival for patients who were subjected to cytoreductive surgery+HIPEC was prolonged for more than 5 months compared with patients who received cytoreductive surgery alone (10.4 vs 15.5 months, p=0.018). In 2011, Zheng Li et al. [20] carried out a meta-analysis on the long-term efficacy in 2,299 patients involving 18 randomized controlled trials in Chinese patients with the following results: the 5-year survival rate in the treatment group was 2.17-fold higher than in the control group, and the recurrence rate was 46% lower than the control group. A Japanese study on the treatment of GIN suggested that the surgical removal of naked-eye visible lesions+HIPEC could significantly improve the long-term survival in locally advanced GIN patients. A Japanese meta-analysis revealed that in 2,145 advanced GIN patients the 1-3 years risk of death in patients who received surgery+ HIPEC was approximately 30% of that in the control group. Overall recurrence rates and peritoneal metastasis rates were significantly lower compared with patients in the control group (OR:0.46-0.47), but the 5-year overall survival difference was not reported. In 2014, researchers from Spain and Ukraine confirmed in their studies that there was a significant survival advantage in GIN patients with peritoneal metastasis who received cytoreductive surgery+HIPEC, compared with patients who received palliative chemotherapy.

In the field of intestinal cancer research, Mingchen et al. conducted a meta-analysis of 8 Chinese papers [20] and reported that in advanced colorectal cancer patients, 3- and 5-year survival rates in those subjected to radical surgery followed by HIPEC were significantly higher (2.13- and 2.39-fold compared with those with radical resection alone, respectively). Some internal control researches revealed that the median survival time or 5-year survival time in patients with peritoneal cytoreductive surgery+HIPEC+systemic chemotherapy was significantly longer than in patients with palliative tumor resection+systemic chemotherapy. Thus, the random control of the clinical trials that Verveal et al. reported

in 2005 [21] had to be stopped midway due to ethical reasons. According to two multi-center, large-sample, and single-group prognosis studies, median survival times of the two groups of locally advanced colorectal carcinoma patients who received cytoreductive surgery+perioperative intraperitoneal perfusion chemotherapy, followed by systemic chemotherapy were 32.4 and 30.1 months, respectively, which were significantly better than the reported efficacy of postsurgical systemic chemotherapy before the application of HIPEC [22,23]. In these studies, the primary predictive factor for mortality risk was the completeness of the cytoreductive surgery and the number of residual lesions in the abdomen. This indicated that patients tolerating radical surgery can benefit most from this treatment method.

In 2013, a 20-year observation study involving 1,000 patients with peritoneal surface implants and metastasis of tumor who received cytoreductive surgery+HIPEC has been reported [24]. Prognostic analysis revealed that median OS was 29.4 months and 5-year survival was 32.5%. Prognostic factors in this study were primary tumor type, preoperative performance status, resection completeness assessment, and treatment experience of the institutions. In 2014, a multi-center multivariate analysis of another large sample prognosis study [25] involving more than 600 peritoneal metastatic carcinoma patients who received cytoreductive surgery+HIPEC revealed that age and peritoneal cancer index were associated with mortality and age, and longer operation time and ascites were related to increased complications.

Although these controlled studies and large-scale survival data have provided sufficient evidence for the combined treatment of cytoreductive surgery plus HIPEC, the results of a study [23] suggested that the success of cytoreductive surgery had a greater impact on patient long-term survival compared with HIPEC or diathermia. Furthermore, the prognostic significance of HIPEC, and especially diathermia, may have not been expected to be so important. In some studies [26,27], HIPEC had even shown no added efficacy. Thus, based on some negative facts (controversial survival advantage, relatively high treatment complications, and nearly 8% mortality), the 2015 colorectal cancer treatment guidelines of NCCN [26] have not recognized HIPEC as a standardized treatment method. However, the NCCN expert group also acknowledged that more clinical trials were required to confirm this treatment approach. Currently, some multi-center randomized controlled trials in phase II and III have been launched [28,29], the results of which would be anticipated. Furthermore, more multiple factor analysis results of retrospective or prospective cohort studies [30,31] have shown the following: preoperative performance status, abdominal tumor diffusion index, completeness of surgical resection and dexterity of HIPEC implementation in various medical institutions are key factors influencing the efficacy of treatment, and the uncertainty of clinical results may originate from these changeable factors. Therefore, the choice of the appropriate population and standardization of diathermic perfusion chemotherapy technology should be the core subject for studies exploring the best efficacy of HIPEC in the future.

Based on the successful experience at home and abroad, in this study we used the cisplatin+5-FU regimen, which is effective in GIN and has a relatively safe dose for intraperitoneal perfusion, aiming at pursuing the best potential therapeutic efficacy of HIPEC. The number of patients with colorectal cancer was the largest in the present study, followed by those with GIN, and most patients were in stages II-III. Excluding patients who were not subjected to radical surgery, all digestive tract tumor patients who received HIPEC in our tumor center enjoyed significantly longer DFS, compared to patients with corresponding features in the control group (median TTP: 40.1 vs 18.5 months, p=0.025). This study has verified the best therapeutic efficacy of HIPEC in patients with complete eradication of visible lesions and these results indicate that HIPEC after radical surgery for GIN can reduce the risk of recurrence, delay tumor progression, and improve the patient quality of life. This is consistent with domestic and foreign research conclusions. At the same time, compared with the control group in our study, adverse reactions and complications in the treatment group showed no significant increase (3 patients in the treatment group had recoverable, incomplete intestinal obstruction, and this was considered to be associated with intraperitoneal chemotherapy, but without statistically significant difference). Tolerance was good.

This study failed to conclude that long-term survival in the treatment group was significantly longer compared with the control group. Except for the reasons that this treatment model may bring uncertainty to the therapeutic results and there was no in-depth assessment on the patient preoperative status, peritoneal tumor index and relevant factors of quality differences in radical surgery, the more possible reasons may be as follows:

1. The follow-up duration was relative short. Among the 55 patients in this study, only 17 were followed-up for 3-years, and the existence of high proportion of censored data resulted in failure of proper estimation of the median survival time. In the treatment group, 13 patients were followed-up for more than 2 years and all of them were surviving, the longest follow-up being 47.5 months. In the control group, 15 patients were followed-up for more than 2 years, and 5 patients died. Although the survival analysis of the two groups resulted in $p>0.05$, the survival curves suggested that survival of patients in the treatment group had an increasing trend. Therefore, with the increase in the number of patients who completed the follow-up, this study may conclude that the long-term survival difference between the two groups might be statistically significant.

2. The timing of HIPEC was relatively delayed because most patients were not informed or fully prepared for receiving intraperitoneal chemotherapy as soon as possible after radical surgery. The treatment strength was likely not enough in some cases. A study [32] revealed that free cancer cells that remained in the peritoneal cavity would incur changes within 24 hrs after the primary cancer lesions were removed. Thus, immediate intraperitoneal perfusion chemotherapy after tumor radical resection is conducive to the killing of intraperitoneal free cancer cells and residual implants. Furthermore, it has several other advantages such as fewer abdominal adhesions in the early postoperative phase, good perfusion tolerance, relatively mild abdominal pain and abdominal distension. In this study, HIPEC was administered to 27 patients in the treatment group more than 2 weeks after radical surgery, which were longer than the treatment timing for many other similar studies, and this may lead to a decline in long-term efficacy. In addition, the local drug concentration of intraperitoneal chemotherapy and the drug delivery area have an important effect on the therapeutic efficacy. Chemotherapy perfusion with high concentrations and in large areas is conducive to the killing of peritoneal free cancer lesions. In this study, in consideration of safety and tolerability, a relative conservative intraperitoneal chemotherapy concentration was adopted and the single perfusion dose of cisplatin was 33 mg/m^2. Furthermore, due to abdominal adhesions, patients were not able to tolerate a perfusate volume more than 1,500 ml. Hence, once this was perfused into the peritoneal cavity through the thermal cycling perfusion machine, the perfusate could not be pumped out and cycled often and this may decrease the efficacy of chemotherapy.

Our study would further validate the long-term survival advantage of HIPEC. Medical professionals should note the importance of HIPEC in the comprehensive treatment of GIN, and strive to improve the overall efficacy of the treatment of GIN after radical operation.

Conflict of interests

The authors declare no confict of interests.

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