Original Article

Laparoscopic distal gastrectomy and hyperthermic intraperitoneal chemotherapy in the treatment of advanced gastric cancer: a retrospective case-matched study on perioperative outcomes

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Background: This study aimed to assess the safety and efficacy of laparoscopic distal gastrectomy (LDG) with intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) for advanced gastric cancer (AGC).

Methods: In this case-matched study, we retrospectively reviewed the database of 223 patients with AGC who underwent LDG in Tangdu Hospital from April 2016 to February 2019. Among all participants, 177 patients underwent LDG alone and 46 underwent LDG with HIPEC. We matched total of 138 (1:2) patients from the LDG + HIPEC group (n 46) and the LDG group (n 92) for gender, age, date of operation, and tumor-node-metastasis (TNM) stage of tumor.

Results: There was no significant difference in the Clavien-Dindo classification of complications between LDG alone and LDG + HIPEC patients. Further analysis showed the morbidity of gastroparesis to be significantly increased in LDG + HIPEC patients. At the same time, we found that the operation time, the time to 1st flatus, and hospital stay were longer in LDG + HIPEC patients and the incidence of abdominal recurrence 2 years after operation was significantly higher in the LDG group than the LDG + HIPEC group.

Conclusions: The combination of LDG with intraoperative HIPEC is a safe and feasible method for AGC and HIPEC will limit the recovery of gastrointestinal functions. In addition, during the follow-up of our study, although there was no statistical difference between the two groups in abdominal recurrence at 2 years after surgery, a decreasing trend of abdominal recurrence in LDG + HIPEC patients could be seen in comparison to LDG patients.

Keywords: Laparoscopic distal gastrectomy (LDG); gastric cancer; hyperthermic intraperitoneal chemotherapy (HIPEC)

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Introduction

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide with 1,033,701 new cases and 782,685 deaths annually (1). While distal gastrectomy with D2-lymphadenectomy remains the gold treatment standard for GC located in the lower or middle third of the stomach, laparoscopic distal gastrectomy (LDG) has gained rapid popularity in recent times and has become

a common operation for early gastric cancer. However, the role of LDG with D2-lymphadenectomy in the treatment of advanced gastric cancer (AGC) remains uncertain. Whilst many researchers have affirmed the improvement in morbidity and mortality of LDG with D2-lymphadenectomy (2-7), its clinical practice is still difficult to carry out and there can be technical difficulties with lymph node dissection and gastrointestinal continuity reconstruction. On the other hand, concerns have been raised about the possible risk of tumor cell shedding and peritoneal implantation because of insufficient lavage in AGC surgery (8), especially in laparoscopic surgery.

Relapse occurs in about 30% of AGC patients treated with gastrectomy and D2-lymphadenectomy, mainly due to distant or peritoneal metastases (PM) (9). Once metastases appear, the median survival is 6.2 months (10). Accordingly, determining how to reduce the risk of recurrence in the peritoneal cavity has become one of the hot spots in GC research. Many studies have demonstrated that hyperthermic intraperitoneal chemotherapy (HIPEC) can prolong the overall survival of patients with peritoneal carcinomatosis in a variety of malignant tumors, including GC (11,12). Mi *et al.* reported that compared with surgery alone, radical gastrectomy with prophylactic HIPEC in AGC patients could safely improve survival rates and reduce recurrence rates (13). van der Kaaij *et al.* designed a prospective multicenter randomized trial to determine the safety, tolerability, and feasibility of gastrectomy combined with HIPEC (14), and a PERISCOPE I study has determined the maximum tolerated dose of intraoperative docetaxel (15). However, the results of these studies are unavailable at this time.

According to some researchers, HIPEC treatment combines the mechanisms of surgical locoregional chemotherapy, hyperthermal therapy, and large-volume abdominal perfusion washing to eradicate residual tumor nodules, micrometastases, and free cancer cells (16-18). In theory, intraoperative HIPEC can also reduce the risk of tumor cell shedding and abdominal implantation in laparoscopic surgery for AGC. However, there are few studies investigating the combination of LDG with HIPEC and it remains unclear whether HIPEC will increase the incidence of postoperative complications seen using LDG during the perioperative period.

We have used LDG with intraoperative HIPEC for AGC patients since 2015, and retrospectively compared the safety and efficacy of using this method with that of using LDG alone over the same period.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-21-20).

Methods

Patients

This retrospective cohort study included 223 patients who underwent D2 standard distal gastrectomy in our institution from April 2016 to February 2019. The patient inclusion criteria were: (I) age 18–70 years old; (II) endoscopic examination and biopsy proven adenocarcinoma of the stomach; (III) T2–T4a tumor according to the 7th edition of the tumor, node, metastasis (TNM) classification system; (IV) expected curative resection via distal subtotal gastrectomy with D2 lymphadenectomy. The exclusion criteria were: (I) distant metastasis or invasion to adjacent organs; (II) local irresectability of the primary gastric tumor; (III) patient unfit for major operation and chemotherapy; (IV) patient was receiving neoadjuvant chemotherapy. Patients were divided into two groups: (I) an LDG + HIPEC group (n 46) who underwent a LDG and HIPEC and (II) an LDG group (n 177) who underwent a LDG alone. Clinical and pathological data were obtained from operative and pathological reports from our institution.

We matched a total of 138 (1:2) patients from the LDG-HIPEC group [46] and the LDG group [92] for gender, age (±5 years), date of operation (±6 mo), and tumor-node-metastasis (TNM) stage of tumor.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Tangdu Hospital, Air Force Medical University and informed consent was taken from all individual participants.

Surgical procedure

Laparoscopic distal gastrectomy with D2 lymphadenectomy was performed in a standard fashion according to the treatment guidelines of the Japanese Gastric Cancer Association (JGCA). Under general anesthesia and hemodynamic monitoring, the patients were placed in a supine position and five ports were inserted into the abdominal cavity, with a transumbilical port used for the camera.

In the LDG group, distal gastrectomy was used for tumors located in the middle and lower third of the stomach.

After lymphadenectomy and gastrectomy, gastrointestinal anastomosis was performed using the instrumental method and a 5 to 7 cm laparotomy was made under the xyphoid to remove the specimen. Reconstruction was performed extracorporeally or total laparoscopically (19).

In the LDG + HIPEC group, after the gastrointestinal continuity reconstruction, an outflow tube (32 F) for perfusion was placed in Douglas' pouch just before HIPEC and two input tubes (22 F) were placed under the left and right diaphragm. HIPEC was performed after closure of the abdominal cavity. All patients undergoing HIPEC were treated with cisplatin as a chemotherapeutic agent, with 120 mg (the dose of cisplatin was 75 mg/m^2) dissolved in 6 L of heated saline (drug concentration of cisplatin 20 μg/mL). After the temperature reached the standard (43 ℃), 50% of the total dose was added to the perfusate, and the remaining drugs were added after one hour. The heated perfusion solution was infused into the peritoneal cavity at a rate of 500 mL/min through two inflow tubes introduced from an automatic hyperthermia chemotherapy perfusion device (BR-TRG-II, BRIGHT MEDICAL). The temperature of the perfusion solution in the peritoneal cavity was kept at 43.0±0.5 ℃ and the total time for HIPEC was approximately 45 min. The perfusion solution was then removed and drainage tubes were placed in Douglas' pouch for 24 hours. The patient was then delivered to the intensive care unit for recovery.

All gastrectomies and HIPEC procedures were performed by a designated team of surgical oncologists, anesthesiologists, and operating room staff in our institution.

Postoperative complications

Surgical complications were stratified using the Clavien-Dindo classification system, which is a compelling tool for quality assessment in surgery.

Postoperative follow-up

Patients were followed up by telephone interview, outpatient review, and WeChat, and the PM status of the patients was determined 2 years after operation. Follow-up results were for the last review due to partial loss of follow-up.

At present, the results of cytology and pathology are considered the gold standard for PM detection. Pathological specimens can be obtained directly through laparoscopy, but this technique is invasive. In addition, due to its lack of specificity in clinical manifestations, small lesion size, and unclear imaging, PM is often difficult to accurately diagnose. Although some patients can be diagnosed by CT, PET/CT and other imaging, cytology, and pathology results, there are still many patients without any clear examination results. Therefore, we comprehensively evaluated whether patients had PM by combining various symptoms and signs, such as reflux, progressive weight loss, decreased appetite, intestinal obstruction, and abdominal distension.

Statistical analysis

The collected data was entered into an electronic database and analyses were performed using SPSS Version 17.0 (SPSS Inc., Chicago, IL, USA). Group comparison of clinicopathological characteristics was performed using analysis of variance for continuous variables and Pearson chi-squared for categorical variables. P value <0.05 was considered to indicate statistical significance.

Results

Enrollment and baseline characteristics

From April 2016 to February 2019, a total of 223 AGC patients were considered for enrollment. After the matching process, 46 patients underwent LDG with HIPEC and 92 underwent LDG. There was no significant difference between the two groups in terms of preoperative characteristics and postoperative pathologic features (*Table 1*).

Short-term outcomes

The operative characteristics of the patients are shown in *Table 2* and the laboratory indexes are shown in *Table 3*. Comparison between the two groups demonstrated no significant difference in blood loss, blood transfusion, time to 1st fluids, and laboratory indexes. Compared with the LDG group, the operation time was significantly increased in the LDG + HIPEC group (P=0.012) and the time to 1st flatus and postoperative stay in the LDG + HIPEC group was obviously longer than in the LDG group.

Complication classification using the Clavien-Dindo system

Complications were graded using the Clavien-Dindo system classification system (*Table 4*). The incidence of

Table 1 Baseline characteristics of study population

Variable	All patients			Match-pairwise patients		
	LDG + HIPEC group	LDG group	P value	LDG + HIPEC group	LDG group	P value
Number of patients (n)	46	177	–	46	92	–
Mean age	52.5±11.22	56.24±9.24	0.173	52.5±11.22	53.26±10.15	0.723
Sex			0.477			Matched
Male	30	125		30	60	
Female	16	52		16	32	
BMI	20.98±5.42	20.95±6.27	0.972	21.67±3.35	22.11±2.83	0.47
Depth of invasion			0.379			Matched
T_2	12	46		12	24	
T_3	16	79		16	32	
T_4	18	52		18	36	
ASA grade			0.314			0.965
I	5	18		5	11	
II	32	139		32	62	
III	9	20		9	19	
NRS2002 score	1.96±0.63	2.18±0.71	0.067	1.96±0.63	2.09±0.69	0.284

LDG, laparoscopic distal gastrectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 2 Comparison of operative characteristics after surgery

Variable	LDG + HIPEC group	LDG group	P value
Operation time (min)	285.56±68.42	255.99±49.5	0.012
Blood loss (mL)	141.94±97.39	128.89±126.6	0.588
Blood transfusion (mL)	50.0±221.04	22.22±132.39	0.185
Time to 1st flatus (d)	4.39±1.55	3.79±1.41	0.048
Time to 1st fluids (d)	5.36±1.77	5.03±1.75	0.356
Postoperative stay (d)	9.75±4.87	8.22±3.22	0.054

LDG, laparoscopic distal gastrectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

overall postoperative complications and postoperative complications of grade 3 or above were not significantly different between the LDG and LDG + HIPEC groups. However, when morbidity was further analyzed, the morbidity of gastroparesis was significantly increased in the LDG + HIPEC.

Follow-up outcomes

As shown in *Table 5*, patients were followed up for an average of 24 months (4–41 months), and the incidence of abdominal recurrence 2 years after operation was significantly higher in the LDG group compared to the LDG + HIPEC group.

Discussion

A lack of research on the use of LDG with HIPEC prompted us to evaluate the feasibility and safety of this method during the perioperative period. Although we

Table 3 Laboratory indexes

Variable	Group	Prior to the operation	One day after surgery	Three day after surgery	Five day after surgery
WBC (10^9/L)	LDG + HIPEC	5.81±1.69	12.53±3.87	9.12±4.08	6.51±4.15
	LDG	6.03±2.06	13.02±4.53	8.47±4.44	5.48±4.17
P value		0.528	0.533	0.407	0.171
HGB (g/L)	LDG + HIPEC	123.63±23.45	115.26±26.3	109.02±29.35	91.52±45.13
	LDG	125.13±25.95	116.57±26.84	101.62±40.07	82.39±53.76
P value		0.742	0.787	0.221	0.296
TP (g/L)	LDG + HIPEC	66.75±8.78	54.35±10.54	56.83±16.37	45.87±26.42
	LDG	67.69±8.31	56.4±10.85	54.53±20.18	43.1±29.22
P value		0.537	0.293	0. 505	0.59
ALB (g/L)	LDG + HIPEC	40.05±4.33	29.09±6.37	30.58±9.04	23.92±14.04
	LDG	40.98±4.41	33.8±26.96	30.07±11.21	23.63±16.2
P value		0.241	0.246	0.791	0.915
AST (μ/L)	LDG + HIPEC	22.65±9.23	78.78±71.41	33.89±29.32	19.89±14.43
	LDG	24.58±12.37	71.47±67.77	35.23±70.05	19.02±19.95
P value		0.353	0.558	0.902	0.793
BUN (mmol/L)	LDG + HIPEC	4.72±1.16	4.36±1.96	5.13±2.64	4.04±3.16
	LDG	5.12±1.43	4.3±1.73	4.03±2.29	3.67±3.04
P value		0.108	0.848	0.012	0.5
Cr (μmmol/L)	LDG + HIPEC	66.18±12.51	64.04±21.32	56.4±23.59	60.03±11.08
	LDG	66.75±15.77	67.13±19.89	58.12±22.77	60.44±14.63
P value		0.833	0.401	0.409	0.877

LDG, laparoscopic distal gastrectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

found that the operation time, the time to 1st flatus, and postoperative stay were longer using LDG + HIPEC, indicating a slower recovery of bowel function, there was no significant difference in the pattern and Clavien-Dindo classification of complications between the two groups. However, when morbidity was further analyzed, the morbidity of gastroparesis was significantly increased in LDG + HIPEC. These results reveal LDG + HIPEC to be a safe and feasible method for AGC although the use of HIPEC will limit the recovery of gastrointestinal function. In addition, during the follow-up, although there was no statistical difference between the two groups in abdominal recurrence at 2 years after surgery, a decreasing trend could be seen in LDG + HIPEC patients in comparison to the LDG group.

It is generally accepted that the presence of PM indicates a poor prognosis in AGC and concerns have been raised that laparoscopic gastrectomy may increase the risk of PM. Some researchers have reported that CO_2 pneumoperitoneum could vaporize GC cells to promote cancer cell scaling and change cancer cell distribution in the peritoneal cavity (20). In addition, gas flow could enhance the invasion and metastasis of cancer cells by influencing the integrity of peritoneal microstructures and promoting exposure of the peritoneal basal layer and expression of relevant adhesion molecules (21-23). The key to preventing PM and improving survival in AGC patients is to eradicate intraperitoneal free cancer cells and micrometastases during and after surgery. Sufficient intraoperative lavage may reduce the peritoneal recurrence rate. In a completed multicenter RCT of 88 microscopic peritoneal metastasis patients who received gastrectomy and D2-lymphadenectomy, peritoneal

Table 4 Complication classification by Clavien-Dindo grade

Complication grade	LDG + HIPEC group	LDG group	P value
Number of patients (n)	46	92	–
Total	6 (13.04%)	11 (11.96%)	1.000
Pattern of complication			
Pancreatic fistula	0	3	0.551
Gastroparesis	3	1	0.108
Pulmonary infection	1	3	1.000
Intraabdominal infection	0	1	1.000
Intraperitoneal hemorrhage	1	0	0.333
Ileus	1	1	1.000
Chylous fistula	0	2	0.552
Clavien-Dindo classification			0.939
Grade 1	1 (2.17%)	2 (2.17%)	–
Grade 2	4 (8.70%)	7 (7.61%)	–
Grade 3	1 (2.17%)	1 (1.09%)	–
Grade 4	0 (0)	0 (0)	–
Grade 5	0 (0)	1 (1.09%)	–

LDG, laparoscopic distal gastrectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

Table 5 Comparison of operative characteristics

Group	Abdominal recurrence 2 years after operation
LDG + HIPEC (n=46)	2 (4.35%)
LDG (n=92)	10 (10.87%)
P value	0.337

LDG, laparoscopic distal gastrectomy; HIPEC, hyperthermic intraperitoneal chemotherapy.

recurrence developed in 40% of patients who received a 10 L lavage and 79% of patients with who received a 3 L lavage (24). However, a large volume of lavage during laparoscopic surgery is often difficult to achieve and may explain the higher incidence of regional or peritoneal recurrence seen in comparison to non-laparoscopic procedures. Many studies have demonstrated that HIPEC can reduce the risk of recurrence or metastasis after surgery and prolong the overall survival of patients (25-27) and this may be because the use of HIPEC effectively performs the same function as lavage.

Yang *et al.* reported that the complication rate of patients who received cytoreductive surgery (CRS) and HIPEC (Cisplatin and Mitomycin C) was 14.29% (5/35) (28), which was similar to that seen in our study (13.04%, 6/46). However, their research involved only a small number of patients. Recently, Glehen *et al.* performed a randomized multicenter phase III study of D2 resection and HIPEC in locally advanced GC (29) and van der Kaaij *et al.* designed a randomized multicenter trial investigating cytoreductive surgery combined with HIPEC (14). However, the results of these two studies are not yet available. The results of our research indicate there was no significant difference in morbidity between the two groups. From the subgroup analysis, we found HIPEC would inhibit the recovery of gastrointestinal tract function, by increasing the rate of gastroparesis and postponing the time of 1st flatus and hospital stay. We consider this to be due to the long duration of hypothermal perfusion and soak of chemotherapy drugs, which leads to the inhibition of digestive tract function. It is well known that there are many risk factors associated with postoperative delayed gastric emptying, such as malnutrition, morbidity

(especially diabetes), pyloric obstruction, psychosocial factors, longer operation time, higher pneumoperitoneum pressure, excessive fluid infusion, and so on. To reduce the incidence rate of gastroparesis, all these factors should be taken seriously during the perioperative period. First of all, the precise preoperative corresponding comprehensive measures should be fully adopted to improve the nutritional status, reduce the edema of gastric wall, and regulate blood sugar to appropriate levels. Besides, for preventing those intraoperative potential factors, personal surgical plan and delicate operation should be made to shorten the operation time, lower pneumoperitoneum pressure should be maintained to perfection, and goal-directed fluid infusion should be conducted to prevent the fluid overload. On the other hand, the use of gastrointestinal motility medications and "false feeding" after surgery may also enhance the recovery of gastrointestinal function to some extent. Indeed, this suggests patients with a high risk for delayed gastric emptying, may not be suitable for HIPEC.

As an aggressive procedure, HIPEC undoubtedly has some side effects, including the redistribution of visceral blood flow which may cause hemodynamic changes, bone marrow suppression associated with chemotherapeutic agents, and some risks of developing other postoperative complications. In our study, no intraoperative hemodynamic instability was found, and the goal-directed fluid infusion and the prophylactic application of vasoactive drugs may be the main reason for well preventing this kind of side effect. Also, no hemopoietic system damaging occurred in postoperative phase for HIPEC group in our study, and nevertheless, blood routine examination of these patients were all monitored more intensively. As for the risks of surgical complications, preventing postoperative bleeding should be a significant concern for us firstly. Intraperitoneal hemorrhage occurred in one patient in the LDG + HIPEC group in our study, and secondary laparoscopy showed the bleeding was at the edge of the mesojejunum (Roux-en-Y anastomosis) and the diameter of the bleeding vessel was about 2 mm. Reviewing our surgical procedure and the principle of HIPEC, we believe this was caused by an ultrasonic scalpel contacting a small mesenteric vessel to fluid mechanical forces during the implementation of HIPEC. This suggests that the HIPEC may increase the risk of postoperative bleeding and the delicate skill should be employed throughout the operation, and ligation clips for vessels above 2mm should be applied. We also retrospectively analyzed the presence of duodenal stump leakage in the LDG group, which suggested that adequate blood supply, residual serosalization, and the avoidance of excessive local duodenal tension may be necessary to avoid leakage from a duodenal stump. For this reason, we adopt some measures such as closing the mesenteric hiatus, closing the Peterson's hiatus, and reinforcing the anastomosis and duodenal stump by suturing the plasmomuscular layer before HIPEC conducting to decrease the risks for ileus and anastomosis leakage.

There are several limitations to this study that may have influenced the outcomes. Firstly, the sample size of the LDG + HIPEC was obviously smaller than that of LDG. The potential for undetected selection bias and lack of long-term follow-up results might also influence the outcome. Secondly, because this was a non-randomized, retrospective study performed at a single center, case selection was inevitably affected by bias. Differences in the postoperative management and discharge criteria may have also led to clinical heterogeneity and a sequence of biases. Thirdly, there was obvious clinical homogeneity in this study due to the inherent flaws of a retrospective cohort study because the baseline levels were not exactly comparable. Differences in the skills of the different surgeons may have also influenced the outcomes. Finally, long-term outcomes were not evaluated because of the short observation period. In the future, randomized controlled trials or prospective cohort studies with long-term follow-up will be necessary to adequately evaluate the status of LDG + HIPEC for gastric cancer.

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Footnote

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of Tangdu Hospital, Air Force Medical University and informed consent was taken from all individual participants.

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