Original Article
Evaluation of early surgical outcomes, acute inflammatory response and oncological outcomes in patients undergo totally laparoscopic distal gastrectomy: a prospective comparision with open distal gastrectomy

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Abstract: *Background and aim:* Totally laparoscopic distal gastrectomy (TLDG) is gradually prevailing in recent years. Improved clinical outcomes have been reported in previous studies. However, the advantages and disadvantages of TLDG in acute inflammatory response, pulmonary function and long-term oncological outcomes remain unclear. This study was conducted to clarify these issues. *Methods:* From March 2010 to September 2011, a total of 74 patients with gastric cancer were perspectively assigned to either TLDG or open distal gastrectomy (ODG). Clinico-pathologic features, operative details, perioperative inflammatory factors, postoperative recovery, and oncological outcomes were compared between the two groups. *Results:* There were 35 patients (25 males and 10 females) received TLDG and 39 patients (29 males and 10 females) received ODG. The two groups were comparable in the clinicopathological characteristics. TLDG had similar operative time, less blood loss, shorter length of hospital stay and equivalent postoperative morbidity as compared to ODG. The reduction of body temperature in TLDG group was larger than ODG group. No significant difference was found between TLDG and ODG in the changes of blood pH value, $PaCO_2$ and WBC count. Elevation of CRP was lower in TLDG than ODG at postoperative 6 h and 24 h. Levels of IL-6 and IL-10 were higher in ODG at postoperative 0 h, 2 h, 6 h and 24 h. During a median follow-up period of 68 months, the overall survival rates and disease-free survival rates had no difference between TLDG and ODG. *Conclusions:* This study demonstrated that TLDG can be safely applied for gastric cancer as well as ODG. TLDG has minimal surgical trauma, milder acute inflammatory response and quicker function recovery. Pneumoperitoneum doesn't adversely affect pulmonary function and oncological outcomes.

Keywords: Laparoscopic gastrectomy, stomach neoplasms, inflammatory response, overall survival rate

Introduction

Gastric cancer (GC) remains one of the most commonly diagnosed malignancies worldwide and the third major cause of cancer-related death globally [1]. Surgery is regarded as a potential option to cure early-stage GC and significantly enhance prognosis in more advanced stage patients [2]. Open gastrectomy (OG) has traditionally been widely used and laparoscopic gastrectomy (LG) has been increasingly performed as a promising approach, showing advantages in many areas such as quicker recovery, less pain, shorter hospitalization, bet-

ter quality of life [3-5]. In addition, studies observing long-term outcomes have shown that carcinoma recurrence rates after laparoscopic resection are comparable to open surgery [6-8].

The most popular version of LG is laparoscopy-assisted distal gastrectomy (LADG), in which, lymph node dissection is completed under the laparoscope. An epigastric auxiliary incision is made to facilitate excision of the specimen and reconstruction of the digestive tract. Another version is totally laparoscopic distal gastrectomy (TLDG), which is characterized by an intra-corporeal anastomosis without auxiliary inci-

sion and no contact with the tumor; it is considered incisionless, with the exception of the trocar wounds.

The minimally invasive advantages of LG appear to be sufficiently demonstrated when analyzing from clinical index alone. Apart from the rapid postoperative recovery, however, postoperative pain, inflammatory stress response and long-term survival status are also critical factors to comprehensively judge the degree of injury caused by a surgical procedure. Therefore, this research has conducted a prospective cohort study comparing TLDG and open distal gastrectomy (ODG) performed in our center during the same period. Indexes such as postoperative pain, inflammatory factor levels and long-term tumor relapse and survival rate between the two groups were compared and analyzed, so as to understand whether TLDG possesses superiority to ODG in terms of the above aspects. Furthermore, TLDG may result in prolonged duration of operation and anesthesia; meanwhile, the long-term intraoperative CO_2 pneumoperitoneum may also exert adverse effect on the internal environment and pulmonary function. Consequently, continuous dynamic monitoring on the intraoperative and postoperative blood gas analysis was also performed on both groups in this research to evaluate such risk.

Materials and methods

Patients

This research was approved by the Zhejiang University's Ethics Committee. A total of 478 consecutive patients underwent radical resection for gastric cancer between March 2010 and September 2011 in our department of Sir Run Run Shaw Hospital. Only patients who agreed to this trial were included in this study and the surgical methods of TLDG or ODG were decided by patients and their families. Written consent was obtained from every patient prior to enrollment. Patients with any of the following conditions were excluded from this prospective non-randomized controlled trial: 1) over 80 years old; 2) palliative resection; 3) subtotal and total gastrectomy; 4) distant metastasis (e.g. peritoneal metastasis or peritoneal lavage cytology positive for carcinoma cells, hepatic metastasis); 5) tumors invading adjacent structures; 6) received neoadjuvant chemotherapy

preoperatively; 7) with the history of gastrointestinal surgery; 8) the score of American Society of Anesthesiologists was 3 or more; and 9) patients with acute inflammation, fever, immune system disorders, and a long history of drugs use with hormones, immunosuppressants, and other effects on the immune system. Thus 35 patients were enrolled in TLDG group and 39 in ODG group. All TLDG procedures were performed by the same surgical team, whereas ODG cases were performed by other two attending surgeons who were proficient in the conventional open surgery.

Outcome measures

The following data were collected: 1) intraoperative effects: operative time, estimated blood loss, number of retrieved lymph nodes (RLNs), proximal and distal margin distance, body temperature; 2) postoperative recovery: pain score, analgesic dosage, time to ambulation, first flatus, restart oral intake, length of postoperative hospital stay (LOS), morbidity and mortality; 3) laboratory examination: pH value, arterial pressure of carbon dioxide ($PaCO_2$), white blood cell (WBC) count, neutrophils percentage (NE%), C reactive protein (CRP), interleukin-6 (IL-6), and IL-10; and 4) oncologic outcomes: recurrence, and survival.

Clinical and pathological staging were determined according to the American Joint Committee on Cancer (the seventh edition), the tumor-node-metastasis (TNM) classification scheme [9]. Intraoperative nasopharyngeal temperature was measured from the beginning of operation and then every 30 minutes a time to the completion of operation. The ambient temperature of the operation room was maintained around 22°C. The fluid used during operation was kept at room temperature before use and other heating measures were not applied during surgery. The intravenous patient-controlled analgesia pump (IPCAP) was routinely used postoperative (gemstar 13000, hospira, USA). The parameter of IPCAP as follow: sufentanil (1 µg/mL), 2 mL of one time dosage, 30 mL of 4 h maximum dosage. The pain score was graded by visual analogue scale (VAS). The VAS was checked at postoperative (PO) 24, 48, 72, 96, and 120 h, the everyday total dosage was also checked at PO 24, 48, and 72 h. The data acquisition was completed by the staff who were independent of this research.

Laboratory examination

The sample of pH and $PaCO_2$ were taken at the end of operation (0 h), PO 2 h, 6 h and 24 h. The sample of WBC, neutrophils and CRP were taken one day preoperatively (pre), PO 24 h, 72 h and 120 h. The sample of IL-6 and IL-10 were taken one day preoperatively (pre), PO 0 h, 2 h, 6 h, 24 h, 72 h and 120 h. WBC, and neutrophils were determined with an automated cell counter (Beckman Coulter Inc. Counter LH 750, USA). pH, and $PaCO_2$ were determined with automation (GEM Premier 3000, USA).The levels of CRP, IL-6, and IL-10 in plasma were measured using ELISA kits (MultiSciences Inc, Shanghai, China), according to the manufacturer's instructions. Samples were collected in ethylene diamine tetraacetic acid (EDTA) anticoagulative tube and were centrifuged within one hour after sampling, the serum separated and then stored at -80°C until analysis of serum cytokines. The serum was centrifuged at 3500 rpm for 10 min.

Biochemical measurements

Double antibody sandwich method was used in our research. Firstly, the anti-human coating antibody was adsorbed onto micro-wells. The antibodies of CRP, IL-6, and IL-10 were adsorbed separately. Then the plasma samples were added so the human CRP/IL-6/IL-10 presented in the sample can bind to antibodies adsorbed to the micro-wells previously. Then biotin-conjugated anti-human CRP/IL-6/IL-10 antibody was added and bound to human CRP/IL-6/IL-10 captured by the first antibody. Horseradish peroxidase (HRP) was added and bound to the biotin-conjugated anti-human VEGF-C antibody. Then substrate solution reactive with HRP was added to the wells and a blue product was formed in proportion to the amount of human CRP/IL-6/IL-10 presented in the sample or standard. The reaction was terminated by addition of acid and the color turned yellow. The optical density (OD) of each cytokines in the samples was determined at 450 nm on a microplate reader (Thermo Fisher Multiskan, USA). Samples were tested in triplicates, and standard curve with human recombinant cytokine was made in each plate.

Surgical procedure

With the patient in the supine position, mobilization of the stomach and en bloc systematic lymph node dissection were performed via five trocars under a pneumoperitoneum. D_2 lymphadenectomy was undertaken according to the rules of the Gastric Cancer Treatment Guidelines 2011 by the Japanese Gastric Cancer Association [9], which included number 7, 8, 9, 10, 11p, 11d, and 12a in addition to the D_1 dissection. Billroth II gastrojejunostomy was performed after resection of the stomach specimen. The details of the surgery are described in our previously published articles [10, 11].

Postoperative management

Patients were supported by total parenteral nutrition (TPN) until they could consume a liquid diet. After the patients could tolerate the liquid diet, they were transferred gradually to a semiliquid diet. To be discharged from the hospital, patients had to be able to tolerate a semiliquid diet and have a normal blood work panel and temperature, with no obvious discomfort. Adjuvant chemotherapy with 5-fluorouracil (5-FU)-based regimens (mostly 5-FU with cisplatin) was recommended to all eligible patients, except those with stage I cancer.

Long-term follow-up

Follow-up data were collected for at least 3 years, including alternating semiannual abdominopelvic CT scans or ultrasound examinations. An endoscopic surveillance was performed annually or earlier if the patient had symptoms or there was any suspicion of recurrence. Recurrence patterns included peritoneal, locoregional, lymph node and hematogenous. Peritoneal recurrences included peritoneal seedlings or Krukenberg's tumors. Locoregional recurrences included tumors in adjacent organs, remnant stomach or anastomoses. Hematogenous recurrences included tumors in other distant sites, such as liver, lung, bone and brain.

Statistical analysis

Quantitative data were expressed as the means ± standard deviations (SD). The Student t-test was used to evaluate continuous variables, and the χ^2 test or the Fisher exact test was applied to evaluate differences in categorical variables. Disease-free survival (DFS) and overall survival (OS) rates were calculated by the Kaplan-Meier method using SPSS software, version 18.0 (SPSS Inc, Chicago, USA).

Table 1. Comparison of the clinicopathological characteristics

Variable	TLDG (n=35)	ODG (n=39)	P value
Age (years)	57.9 ± 10.4	60.3 ± 11.4	0.36
Gender (M/F)	25/10	29/10	0.80
BMI (kg/m^2)	22.4 ± 3.2	22.5 ± 3.3	0.84
Comorbidities (Y/N)	11/24	14/25	0.69
Hypertension	6	8	
Diabetes mellitus	3	5	
Cardiovascular	0	1	
Pulmonary	2	1	
Others	1	0	
ASA (I/II)	23/12	24/15	0.81
Tumor size (cm)	3.6 ± 1.4	4.0 ± 1.6	0.24
TNM (I/II/III)	21/5/9	15/14/10	0.06

M: male, F: female, Y: yes, N: no, BMI, body mass index, ASA: the American Society of Anesthesiologists, TNM: tumor-node-metastasis.

Table 2. Comparison of intraoperative effects and postoperative recovery

Variable	TLDG (n=35)	ODG (n=39)	P value
Operation time (min)	206.5 ± 33.2	217.1 ± 33.7	0.18
Blood loss (mL)	110.3 ± 57.8	237.4 ± 74.9	<0.01
RLN	27.7 ± 8.1	30.6 ± 9.1	0.15
Proximal margin (cm)	5.8 ± 1.0	5.9 ± 1.3	0.74
Distal margin (cm)	5.4 ± 0.8	5.0 ± 1.8	0.23
Ambulation (days)	1.9 ± 0.7	2.4 ± 1.0	0.03
Flatus (days)	3.1 ± 0.8	3.9 ± 0.9	<0.01
Oral intake (days)	4.3 ± 0.9	5.4 ± 1.6	<0.01
LOS (days)	9.0 ± 2.5	10.8 ± 2.7	<0.01
Morbidity (yes/no)	6/29	6/33	0.84

RLN: retrieved lymph node, LOS: length of postoperative hospital stay.

DFS was defined as the time from surgery to the time of recurrence of the original gastric cancer or development of a second malignancy. OS was defined as the time from surgery to date of death from any cause. P<0.05 was considered statistically significant.

Results

Clinicopathological characteristics

There was no significant difference between TLDG and ODG regarding age, sex, BMI, ASA, tumor size, and TNM stage. There were 35 cases (25 males and 10 females) included in the TLDG group with a mean age of 57.9 years,

whereas 39 cases (29 males and 10 females) included in the ODG group with a mean age of 60.3 years. In the TLDG group, pathologic examination revealed 21 (60.0%) patients with stage I, 5 (14.3%) with stage II, and 9 (25.7%) patients with stage III tumors. In the ODG group, the numbers of patients with stage I, II, and III were 15 (38.5%), 14 (35.9%), and 10 (25.6%) respectively. Although the percentage of advanced cases was higher in ODG group, the difference did not reach statistical significance (P=0.06). The clinicopathological characteristics of TLDG and ODG were summarized in **Table 1**.

Intraoperative effects

Compared with ODG, TLDG had comparative operative time (206.5 ± 33.2 vs. 217.1 ± 33.7 min, P=0.18). The intraoperative blood loss was significantly less in TLDG group (110.3 ± 57.8 vs. 237.4 ± 74.9 ml, P<0.01). The difference in the mean number of RLNs between TLDG and ODG was not significant (27.7 ± 8.1 vs. 30.6 ± 9.1, P=0.15), as were the length of proximal and distal resection margin. The outcomes of intraoperative effects were summarized in **Table 2**.

Every points of the body temperature all continued to decrease with the following time in two groups (**Figure 1**). The reduction of temperature in TLDG group was larger than ODG group and the differences were statistically significant at four time points (30 min, 60 min, 90 min and 180 min) after surgery beginning.

Postoperative recovery

The time to ambulation, first flatus, restart oral intake, and LOS were significantly shorter in TLDG group than that in ODG group (P<0.01, **Table 2**). VSA scores were significantly lower in TLDG group than that in ODG group (P<0.05), in which only PO 24 h without reaching statistical significance (P=0.07). Meanwhile, the dosage of IPCAP was significantly lesser in TLDG group than that in ODG group at PO 24, 48 and 72 h. The postoperative VSA scores and dosage of painkiller were listed in **Table 3**.

The rate of postoperative morbidity in TLDG group was 17.1% (6/35 patients), and there
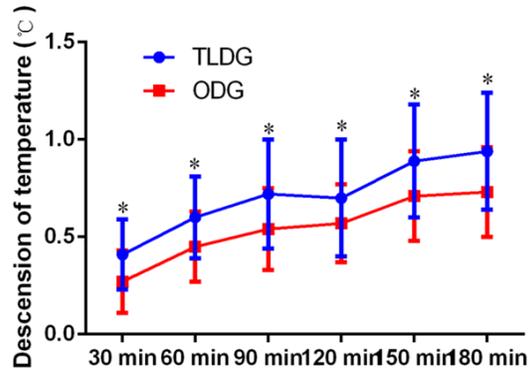
Figure 1. Evaluation of the intraoperative changes in the body temperature. *P<0.05.

Table 3. Comparison of the postoperative VSA scores and dosage of painkiller

Variable	TLDG (n=35)	ODG (n=39)	P value
VSA score			
PO 24 h	2.7 ± 0.7	3.1 ± 1.1	0.07
PO 48 h	2.3 ± 0.5	2.6 ± 0.7	0.03
PO 72 h	2.1 ± 0.5	2.4 ± 0.8	<0.01
PO 96 h	1.8 ± 0.6	2.2 ± 0.5	<0.01
PO 120 h	1.6 ± 0.7	2.1 ± 0.5	<0.01
IPCAP usage (mL)			
PO 24 h	34.1 ± 23.0	62.5 ± 39.8	<0.01
PO 48 h	24.0 ± 16.0	47.1 ± 31.4	<0.01
PO 72 h	9.5 ± 8.2	26.4 ± 28.2	<0.01

PO: postoperative, VAS: visual analogue scale, IPCAP: intravenous patient-controlled analgesia pump.

was no perioperative mortality. Incidences of morbidity included one case of anastomotic leakage at the gastrojejunostomy site (requiring an operative correction) and one case of hemorrhage from gastroduodenal artery (requiring an operation to stop the bleeding). Other complications included abdominal abscess (n=2), pulmonary infection (n=1), and hypoproteinemia (n=1). In ODG group, one case of delayed hemorrhage from hepatic artery required an emergency operation. Unfortunately, the patient died of disseminated intravascular coagulation (DIC) on PO 35 days. There was also a case of anastomotic leakage requiring an operative correction. Other complications in ODG group included pulmonary infection (n=3), wound infection (n=1), and delayed gastric emptying (n=1). The postoperative mor-

Table 4. Comparison of blood gas analysis outcomes within postoperative 24 hours

Variable	TLDG (n=35)	ODG (n=39)	P value
pH			
PO 0 h	7.37 ± 0.05	7.36 ± 0.04	0.86
PO 2 h	7.35 ± 0.03	7.35 ± 0.03	0.79
PO 6 h	7.36 ± 0.02	7.36 ± 0.03	0.84
PO 24 h	7.36 ± 0.04	7.36 ± 0.04	0.97
$PaCO_2$ (mmHg)			
PO 0 h	38.0 ± 5.5	37.9 ± 6.0	0.92
PO 2 h	39.9 ± 4.4	40.1 ± 4.4	0.80
PO 6 h	38.2 ± 3.5	37.9 ± 3.2	0.65
PO 24 h	38.5 ± 4.5	38.4 ± 4.2	0.97

PO: postoperative.

bidity was not statistic different between two groups (14.5% *vs.* 15.4%, P=0.84).

Blood gas analysis

The blood gas analysis after surgery completion (0 h, 2 h, 6 h, 24 h) in the TLDG and ODG groups were listed in **Table 4**. The results showed that pH value and $PaCO_2$ were all within the normal level, and there were no significant different in every points between two groups.

Inflammatory responses

The change trends of WBC between the two groups were similar. WBC level was significantly increased, reaching the peak at PO 6 h, and then decreased gradually. The total WBC count was lower in the TLDG group than in the ODG group. As to every points, however, there were no statistically different except that the TLDG group in PO 6 h was significant lower than ODG group (P<0.05) (**Figure 2A**).

The change trend of NE% was similar to that of WBC. However, even though the NE% level of PO 0 h in the TLDG group was lower than that of in the ODG group, the difference was not statistically significant (P=0.06, **Figure 2B**).

The increase of CRP was significant after surgery in both groups. The time of reaching the peak was PO 72 h and PO 24 h in the TLDG and ODG group, respectively. The difference was statistically significant in the TLDG group compared with that in the ODG group at PO 6 h and PO 24 h (P<0.05, **Figure 2C**).
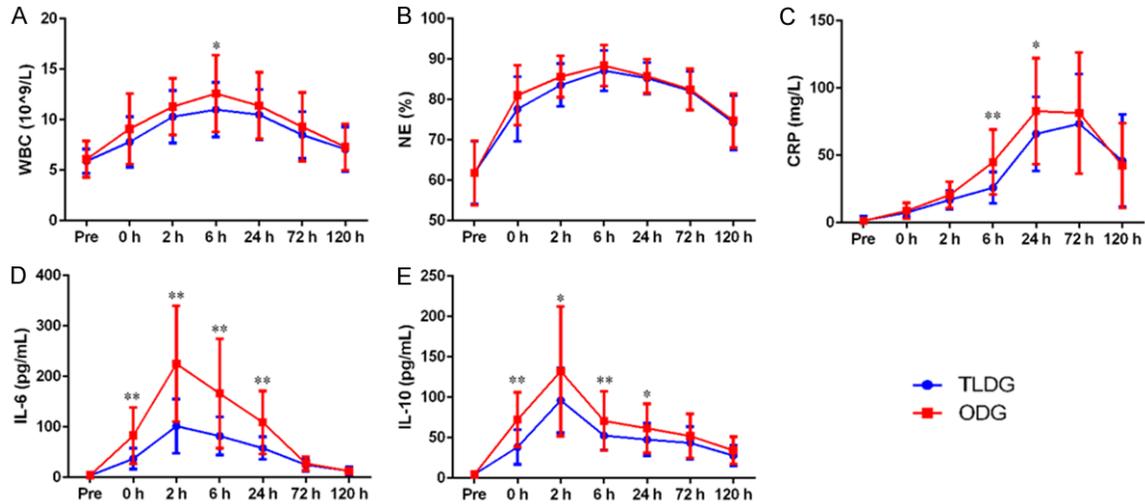
Figure 2. Evaluation of the postoperative inflammatory response changes: (A) WBC; (B) NE; (C) CRP; (D) IL-6; (E) IL-10. *P<0.05, **P<0.01.
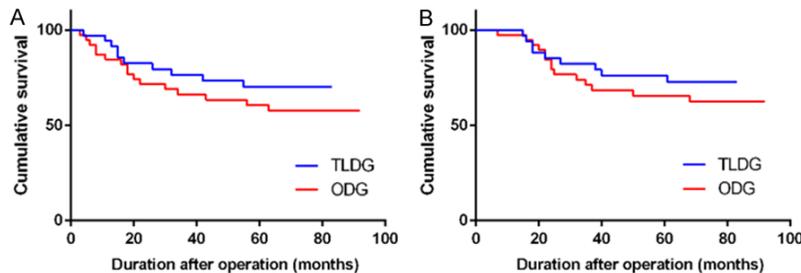
Figure 3. Kaplan-Meier survival curves: (A) Cumulative DFS; (B) Cumulative OS.

The level in the two groups increased significantly after surgery, and peaked at PO 2 h and then decreased gradually. The level of increase was significantly lower in the TLDG group with ODG group. The difference of increased IL-6 was statistically significant in the TLDG group compared with ODG group at PO 0 h, 2 h, 6 h, and 24 h (P<0.05) (**Figure 2D**).

The level also peaked at PO 2 h in both group. Levels was significantly lower in the TLDG group comparing with ODG group at PO 0 h, 2 h, 6 h, and 24 h (P<0.05) (**Figure 2E**).

Recurrence and survival

The median follow-up period for the TLDG group was 68 (range, 13-83) months and 68 (range, 7-92) months for the ODG group. Two cases in TLDG group and three cases in ODG group were lost to follow-up assessment. Nine patients developed tumor recurrence in TLDG group, 3

(33.3%) peritoneal recurrence, 2 (22.2%) distant or hematogenous recurrence, 2 (22.2%) lymphatic recurrence and 2 (22.2%) locoregional recurrence. Of these patients, 8 died of gastric cancer recurrence, and 1 patient are still alive with disease at closure date. Two other patients died due to causes other than gastric cancer. There were 16 cases of recurrence and 14 deaths in ODG group. The sites of recurrence were 5 (31.3%) peritoneal recurrence, 5 (31.3%) distant or hematogenous recurrence, 3 (18.8%) lymphatic recurrence and 3 (18.8%) locoregional recurrence. The 3-y and 5-y DFS rate was 76.5% and 70.1% in TLDG, 66.3% and 60.5% in ODG (**Figure 3A**). The 3-y and 5-y OS rate was 82.2% and 76.2% in TLDG, 71.2% and 65.6% in ODG (**Figure 3B**). The differences of survival rates were not statistically significant between groups (DFS, P=0.28; OS, P=0.39).

Discussion

Totally laparoscopic distal gastrectomy (TLDG), which is characterized by an intracorporeal anastomosis without auxiliary incision and no contact with the tumor, is considered incisionless, with the exception of the trocar wounds. The available clinical evidences implied that

TLDG could be a feasible alternative to LADG for gastric cancer performed in experienced hands, especially favored in patients with a high body mass index [12-16]. Therefore, the present study was a prospective cohort study with long-term follow-up to provide a relatively objective evaluation of TLDG.

The intraoperative hypothermia exerts numerous adverse effects on recovery like inducing cardiovascular diseases, increasing the risk of wound infection and prolonging postoperative length of stay [17, 18]. ODG is a major abdominal surgery with long-term exposure of organs in the air and consequently loss of heat. Meanwhile, some concerns of hypothermia also arise from laparoscopic surgery. First of all, prolonged duration of anesthesia is associated with the severity of hypothermia [19]. Identical relationship was observed in both ODG and TLDG in our study. Laparoscopic surgery consumes longer operative time in set of most abdominal surgeries [20]. But in this study, TLDG could perform in a comparative time to ODG do. Pneumoperitoneum also results in transitory retention of CO_2, compensative hyperventilation and heat loss. More importantly, the gas would spill and take away heat during introduction and withdraw of laparoscopic instruments and aspiration. As showed in research, the application of dry-cold CO_2 was the primary cause, which was responsible for a great amount of heat loss [21]. Consequently, application of heated and humidified CO_2 could effectively prevent the problem of body temperature decrease in laparoscopic surgery [22, 23]. Our study showed that in same operative time, patients underwent TLDG had higher reduction of temperature. The trend could be seen even only 30 min after the initiation of surgery, which had lasted until the completion of surgery. Therefore, we believed that TLDG was more likely to induce intraoperative hypothermia in the absence of insulation measure. Studies suggested that laparoscopic surgery would not lead to more severe hypothermia [24-26]. However in these studies, researchers mostly drew their conclusions based on simple surgeries like laparoscopic cholecystotomy (LC) or using intraoperative application of insulation measure in their study [24-26]. In later clinical practice, we take some insulation measure, including application of cutaneous warming systems, avoidance of unnecessary aspiration.

Furthermore, continuous CO_2 pneumoperitoneum might cause additional burden on pulmonary function. According to our experience, the intraoperative end-tidal CO_2 ($ETCO_2$) could be maintained within a normal range. Blood-gas was dynamically monitored in both groups within 24 h after surgery, and the results indicated that the differences in postoperative pH and $PaCO_2$ between groups were not statistically significant. Thus, it could be seen that a reasonable setting of ventilator contributed to completely eliminating the adverse effects of long-term CO_2 pneumoperitoneum on pulmonary function. Chang *et al.* reported the changes in $ETCO_2$ and $PaCO_2$ during LG were significant in patients comorbid with chronic obstructive pulmonary disease (COPD) [27]. However, in our study, there was no significant difference in incidence of postoperative pulmonary complications between the laparoscopic or open surgery.

As to intraoperative effects and postoperative recovery, the present study demonstrated that blood loss, ambulation, time to flatus and oral intake in TLDG group were significantly superior than that in ODG group, whereas operative time, morbidity and mortality, resection of lymph nodes and proximal resection margin were comparable between two groups. These findings met the majority studies of laparoscopic gastric surgery [28-31]. Besides, in our opinion, the operative time of TLDG in experienced hands could be similar to ODG owing to the application of automatic staples in TLDG. In terms of postoperative pain, results indicated that pain control in TLDG group was superior even in the presence of reduced postoperative dosage of painkiller. It sufficiently suggested that TLDG possessed huge advantage in relieving postoperative pain, which mainly benefited from its smaller surgical incision.

Our results indicated that all inflammatory factors in both groups were markedly elevated postoperatively, which were notably higher than preoperative levels even until 120 h after surgery. It could be figured out that both groups developed obvious inflammatory stress response postoperatively, which had lasted for a long time. Comparative analysis between two groups suggested that IL-6, IL-10 and CRP levels in TLDG group were notably lower than those in ODG group within 24 h after surgery.

On the contrary, the differences between two groups were not significant postoperative 72 h. Cui *et al.* found no statistical differences between laparoscopy-assisted gastrectomy (LAG) and OG for gastric cancer patients with respect to the levels of perioperative cytokines, such as IL-4, IL-6. However, cytokines in the LAG group had trends to return to preoperative levels faster than OG group [32]. Therefore, we believe that laparoscopic surgery could contribute to alleviating the inflammatory stress response in early time after surgery, but such advantage gradually disappeared with time passing due to the homeostasis system. In this study, postoperative WBC count and NE% in both groups were also compared. The results revealed that WBC count and NE% in TLDG group were distinctly lower than those in ODG immediately after surgery (PO 0 h), but no significant differences could be seen between two groups at the remaining points. Okholm *et al.* in their review found that IL-6 and CRP were significantly reduced in laparoscopic patients compared to laparotomy for gastric cancer [33]. However, although most included studies reported low levels of WBC in laparoscopic patients, this result did not reach statistical significance. These studies suggested that when evaluating inflammatory stress level in patients, WBC and NE% can't reflect the delicate difference as IL-6, IL-10 and CRP. In addition, Lee *et al.* reported that postoperative WBC and CRP level in the TLDG group were significantly lower than those in the LADG group for gastric cancer [34], which was different from our previous retrospective study [13]. Therefore, whether TLDG could further reduce inflammation compared to LADG need future research with more cytokines to confirm.

Cancer recurrence and long-term survival are two critical outcomes for evaluating surgical interventions in oncological therapy. The extent of lymph nodes dissection and the number of harvested lymph nodes are the main index to judge the curative effect. Researches including this study revealed that the laparoscopic approach was able to achieve the same outcomes both in early and advanced gastric cancer [7, 8, 35, 36]. There was a concern that pneumoperitoneum was a risk for recurrence of gastric cancer [37], especially in patients with serosa-invasived tumors [38]. On the other hand, Son *et al.* argued LG can safely applied in patients even with serosa-positive tumors [39].

Mo *et al.* conducted a meta-analysis of 20 randomized control studies (RCTs) and demonstrated pneumoperitoneum does not enhance wound metastases following various laparoscopic abdominal surgeries [40]. In our study, we also found TLDG had a similar incisional recurrence risk as ODG. In addtion, it was reported that the immune function played an important role in the recovery, and prevent metastasis and recurrence [41]. Li *et al.* [42] reported laparoscopic surgery was associated with low IL-6, IL-8 secretion and less circulating tumor cells (CTCs), suggesting the advantages in restricting CTCs release and preserving immune response for hepatocellular carcinoma (HCC) patients. Lee *et al.* [8] performed a retrospective study of 2410 patients comparing LADG with ODG for gastric cancer by propensity-score matching analysis finding that 5-year OS rates were not significantly different. In our study, the median follow-up duration was as long as 68 months. We found that TLDG was not inferior to ODG without statistical significant in DFS or OS between the two groups.

Our study shows that TLDG is associated with the advantages of minimal surgical trauma, milder acute inflammatory response and quicker function recovery. Pneumoperitoneum doesn't have an adverse effect in patients' pulmonary function and oncological outcomes. However, regarding the inherent limitation of our study, well designed large scale randomized study is needed to further confirm the advantages of TLDG.

Acknowledgements

Disclosure of conflict of interest

None.

Abbreviations

TLDG, Totally laparoscopic distal gastrectomy; ODG, Open distal gastrectomy; GC, Gastric cancer; OG, Open gastrectom; LG, Laparoscopic gastrectomy; LADG, Laparoscopy-assisted distal gastrectomy; RLN, Retrieved lymph node; LOS, Length of postoperative hospital stay; PaCO$_2$, Arterial pressure of carbon dioxide; WBC, White blood cell; NE, Neutrophils; CRP, C reac-

tive protein; IL, Interleukin; TNM, Tumor-node-metastasis; IPCAP, Intravenous patient-controlled analgesia pump; PO, Postoperative; VAS, Visual analogue scale; h, hour; pre, Preoperative; EDTA, Ethylene diamine tetraacetic acid; OD, Optical density; HRP, Horseradish peroxidase; TPN, total parenteral nutrition; 5-FU, 5-fluorouracil; SD, Standard deviation; DFS, Disease-free survival; OS, Overall survival; LC, Laparoscopic cholecystotomy; $ETCO_2$, End-tidal CO_2; COPD, Chronic obstructive pulmonary disease; LAG, Laparoscopy-assisted gastrectomy; RCT, Randomized control study; CTC, Circulating tumor cell; HCC, hepatocellular carcinoma.

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