Observational Study

Risk factors for postoperative delayed gastric emptying in ovarian cancer treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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after CRS-HIPEC. The median age and body mass index of all patients were 59 years and 22.83 kg/m², respectively. Preoperative chemotherapy was administered in 55 patients (71%). Sixty-two patients (81%) had a history of at least one previous pelvic surgery. The median operation time and intraoperative hemorrhage volume were 630 min and 600 mL, respectively. Omectomy was performed in 32 cases of primary ovarian cancer and 24 cases of recurrence. The median peritoneal cancer index was 16. The risk factors for delayed gastric emptying from the univariate analysis were body mass index < 23 kg/m² ($X^2 = 5.059$, $P = 0.025$), history of pelvic surgery ($X^2 = 4.498$, $P = 0.034$), history of chemotherapy ($X^2 = 4.334$, $P = 0.037$), operation time ≥ 7 h ($X^2 = 4.827$, $P = 0.047$), and intraoperative hemorrhage ≥ 800 mL ($X^2 = 7.112$, $P = 0.008$). Multivariable analysis revealed that age ≥ 70 years (HR = 7.127; 95%CI 1.122-45.264; $P = 0.037$) and intraoperative hemorrhage ≥ 800 mL (HR = 3.416; 95%CI 1.067-10.939; $P = 0.039$) were independently associated with postoperative delayed gastric emptying after CRS-HIPEC.

CONCLUSION
Postoperative gastrointestinal management, including prolonged nasogastric intubation, should be promoted for patients over 70 years or those with intraoperative bleeding exceeding 800 mL.

Key Words: Delayed gastric emptying; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Ovarian cancer; Complication; Nasogastric tube

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Core Tip: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are alternatives for ovarian cancer. Delayed gastric emptying (DGE), a common complication of this procedure, can cause discomfort and decrease quality of life postoperatively. However, little attention has been paid to this complication. Identifying patients at increased risk for DGE may aid patient selection as well as postoperative gastrointestinal management. A retrospective study was conducted, and risk factors for DGE were analyzed using univariate and multivariate analyses. We found that age ≥ 70 years and intraoperative hemorrhage ≥ 800 mL were independently associated with postoperative delayed gastric emptying after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy.

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INTRODUCTION
Ovarian cancer, which has the highest mortality rate among gynecological malignancies in developed countries, is the seventh most common cancer in women globally, with 5-year survival rates below 45%.[1,2] Approximately 70% of cases are diagnosed at an advanced stage, and more than 60% of patients experience recurrence, though with a good initial response to treatment[3].

In recent years, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) has emerged as an alternative treatment for ovarian cancer. Controversies still exist as to whether CRS-HIPEC can further improve the prognosis of ovarian cancer patients when compared with CRS alone. Some studies have shown promising results, and the morbidity and mortality rates of CRS-HIPEC are directly comparable to those of surgical oncology procedures of similar extent[4-8]. The procedure involves a considerable proportion of bowel resection and anastomosis. Much more attention has been given to organic lesions, such as intestinal
perforation, fistula and mechanical ileus, than to delayed gastric emptying (DGE), a kind of functional gastroparesis.

DGE, a common complication after abdominal surgery, can cause discomfort and decrease quality of life postoperatively. Characterized according to the definition of the International Study Group of Pancreatic Surgery, DGE can be classified into grades A, B, and C by its clinical impact[9]. Only grades B and C are regarded as clinically relevant[9,10]. Though not a life-threatening complication, DGE can increase the duration of postoperative hospitalization and hospital costs, decrease quality of life, and even affect long-term prognosis. However, few studies have focused on DGE in ovarian cancer patients after CRS-HIPEC.

The aim of this study was to identify the risk factors for DGE in patients with advanced and recurrent ovarian cancer treated with CRS-HIPEC. Identifying patients at increased risk for DGE may aid patient selection as well as postoperative gastrointestinal management.

MATERIALS AND METHODS

Patient selection
From March 2014 to April 2018, 77 patients with pathologically diagnosed advanced and recurrent ovarian cancer treated by CRS-HIPEC at the Department of Peritoneal Cancer Surgery and Gynecology, Beijing, China, were enrolled in this study. The major inclusion and exclusion criteria, as well as preoperative evaluations, have been previously reported[11] and were strictly implemented in this study to minimize bias. All patients provided written informed consent before enrollment, and the study was approved by the ethics committee and institutional review board.

CRS-HIPEC procedure
The extent of peritoneal spread was assessed after abdominal exploration using the peritoneal cancer index (PCI). Then maximal CRS was performed including primary tumor removal, complete resection of the tumor nodule with intestinal resection if necessary, and peritoneectomy. The gastroepiploic artery was preserved during omentectomy to minimize the effect on gastric emptying, although there it has been reported that there is no association between preservation of the gastroepiploic artery during omentectomy and gastric emptying after CRS-HIPES[12]. The completeness of cytoreduction was evaluated for each patient with a standardized cytoreduction scoring system[13]. HIPEC was then implemented using the open coliseum technique, the details of which have been described elsewhere, and all CRS-HIPES procedures were based on Sugarbaker’s principles[14,15].

Definition of clinically relevant postoperative DGE
Clinically relevant postoperative DGE was defined as a nasogastric tube (NGT) left in place for ≥ 8 d or < 8 d but repeated emesis after removal of the NGT and/or need for reinsertion of the NGT or failure to tolerate unlimited oral intake by postoperative day 14[9,10].

Parameters observed in the study
The demographic data included age, body mass index (BMI), concomitant disease, preoperative chemotherapy, serum cancer antigen 125 (CA-125) level, and pleural effusion status. During CRS-HIPEC, we collected information about the operation time, PCI, intraoperative bleeding, number of organs removed, intestinal resection and anastomosis. The NGT intubation time and eating status were recorded after CRS-HIPEC.

Statistical analysis
The data were included in a prospective database established at the beginning of the surgery and were analyzed using SPSS software (version 18.0; SPSS incorporated, an IBM Company, Chicago, IL, United States). Data from 77 patients, without any missing data, are expressed as the median (range) and frequency. Univariate analyses were comparing patients who experienced DGE with patients who did not were performed using chi-square tests. A 95%CI (P < 0.05) was considered statistically significant. All of the statistically significant variables in the univariate analysis were entered into the multivariable logistic regression model to determine factors independently associated with DGE.
A statistical review of the study was performed by a biomedical statistician.

**RESULTS**

**Demographic data and surgical characteristics**

A total of 77 patients with pathologically confirmed ovarian cancer were enrolled in this study, with a median age of 59 years (range: 35-79 years). The median BMI of all patients was 22.83 kg/m$^2$ (range: 13.8-33.98). In total, 10% of the patients had diabetes mellitus, and 21% had high blood pressure. Preoperative chemotherapy was administered in 55 patients (71%), with an average number of 6 chemotherapy cycles per patient (range: 0 to 25 cycles). Cytoreductive surgery plus HIPEC was indicated in 32 patients (42%) with primary ovarian cancer and in the remaining 45 patients (58%) for recurrent disease. Sixty-two patients (81%) had a history of at least one previous pelvic surgery. The median serum CA-125 level was 277.2 U/mL (range: 7.2-10001.0 U/mL). The demographic data are shown in Table 1.

Table 2 summarizes the CRS-HIPEC characteristics. The median operation time and intraoperative hemorrhage volume were 630 min (range: 280-960) and 600 mL (range: 50-5000), respectively, with 69% of patients undergoing bowel resection. Omectomy was performed in 32 cases of primary ovarian cancer and 24 cases of recurrence. The median PCI was 16 (range: 1-39), and 78% of patients underwent optimal cytoreductive surgery. The most commonly used chemotherapeutic agent was docetaxel, alone or in combination with carboplatin and mitomycin.

**Univariate analysis of risk factors associated with DGE after CRS-HIPEC**

The incidence rate of DGE was 36% (28/77). Univariate analysis found a BMI < 23 kg/m$^2$ ($P = 0.025$), no history of pelvic surgery ($P = 0.034$), fewer than 7 previous chemotherapy cycles ($P = 0.037$), operation time ≥ 7 h ($P = 0.047$) and intraoperative hemorrhage ≥ 800 mL ($P = 0.008$) to be associated with an increased rate of DGE (Table 3).

Patients who underwent gastrectomy, pancreatectomy, splenectomy, and left total diaphragmatic peritonectomy were divided into perigastric and gastric dissection groups. Perigastric and gastric dissection is known to be the greatest risk factor for DGE. However, it was not found to be related to DGE by univariate analysis ($P = 0.421$) in this study.

**Multivariate analysis of risk factors associated with DGE after CRS-HIPEC**

Age and all of the statistically significant variables in the univariate analysis, including BMI, history of pelvic surgery, number of previous chemotherapy cycles, operation time and intraoperative hemorrhage, were entered into the multivariable logistic regression model to determine factors independently associated with DGE.

We found age ≥ 70 years (odds ratio [OR] = 7.127, 95% CI: 1.122-45.264, $P = 0.037$) and intraoperative hemorrhage ≥ 800 mL (OR = 3.416, 95% CI: 1.067-10.939, $P = 0.039$) to be independent risk factors for DGE after CRS-HIPEC in advanced and recurrent ovarian cancer patients (Table 4).

**DISCUSSION**

Ovarian cancer, which generally presents at an advanced stage, is the most common cause of death due to a gynecological cancer[16]. After standard treatment, including cytoreductive surgery and systemic chemotherapy, the peritoneal surface is usually the primary site of disease recurrence, and the prognosis of these patients is poor when treated with conventional systemic chemotherapy. Thus, cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy has been developed, achieving longer recurrence-free survival and overall survival than surgery alone, and the side effect rate is acceptable[11].

The incidence of adverse events of CRS-HIPEC administered in ovarian cancer ranges from 15% to 66% and mainly includes anastomotic leakage, abdominal abscess, intestinal obstruction, pleural effusion, and hematological toxicity[11,17]. Delayed gastric emptying, a frequent intestinal adverse effect, is frequently overlooked and can affect the quality of life of patients, prolong the length of hospital stay, and even affect long-term prognosis. The aim of this study was to identify the risk factors for clinically relevant DGE in patients with advanced and recurrent ovarian cancer treated with
### Table 1 Patients data (n = 77)

| Characteristic                                           | Value                        |
|----------------------------------------------------------|------------------------------|
| Age (yr, median and range)                               | 59 (35-75)                   |
| BMI (kg/m², median and range)                            | 22.83 (13.8-33.98)           |
| Concomitant disease, n (%)                               |                              |
| Diabetes mellitus                                        | 8 (10)                       |
| High blood pressure                                      | 16 (21)                      |
| History of chemotherapy (cycles, median and range)       | 6 (0-25)                     |
| Pelvic surgical history, n (%)                           | 62 (81)                      |
| Serum CA-125 level (U/mL, median and range)              | 277.2 (7.2-10001.0)          |
| Primary/recurrent ovarian cancer, n (%)                  |                              |
| Primary                                                  | 32 (42)                      |
| Recurrent                                                | 45 (58)                      |
| FIGO stage for primary ovarian cancer (n)                 |                              |
| IIIB                                                     | 7                             |
| IIIC                                                     | 4                             |
| IVB                                                      | 21                            |
| Histology, n (%)                                         |                              |
| Serous                                                   | 55 (71)                      |
| Others                                                   | 22 (29)                      |

BMI: Body mass index.

The pathophysiology behind delayed gastric emptying has proven to be complicated, with multiple variables involved. In our analysis, we found that age ≥ 70 years and intraoperative hemorrhage ≥ 800 mL were independent risk factors for DGE after CRS-HIPEC in advanced and recurrent ovarian cancer patients. With increasing age, gastrointestinal function gradually weakens; thus, older people were more susceptible to DGE. The other risk factor associated with DGE was intraoperative hemorrhage. The specific mechanism of how blood loss affects DGE is not clear. We hypothesize that the blood redistributes with an increase in hemorrhage; hence, the gastric mucosa becomes ischemic, weakening gastrointestinal motility.

Perigastric and gastric dissection is known to be the greatest risk factors for DGE. However, it was not found to be related to DGE in our study (\(P = 0.421\)). The DGE rate in the perigastric and gastric dissection group was 46.2% (6/13), higher than that in the group without perigastric or gastric dissection (34.4%, 22/64). The possible reason for this may be that the sample size is too small. Perhaps there will be a significant difference between the two groups as the number of cases increases.

Delayed gastric emptying is a main complication after CRS-HIPEC with unknown origin in ovarian cancer. Extensive intestinal manipulation, intraperitoneal chemotherapy, and intraperitoneal hyperthermic perfusion during surgery are all plausible causes of this phenomenon. The definition of postsurgical delayed gastric emptying was uncertain and varied in different reports before an objective and generally applicable definition of DGE was developed by the International Study Group of Pancreatic Surgery[9]. Based on severity and clinical impact, DGE was classified into grades A, B, and C. Only grades B and C are regarded as clinically relevant and were studied in this study. Nausea caused by anesthesia, wound pain, stimulation from the nasogastric tube and so on are sometimes difficult to distinguish from nausea caused by DGE. However, the severity, duration and clinical impact of nausea caused by the above reasons usually cannot match the levels of DGE in grade A or B. Thus, these causes of nausea were not studied here.

Treatments for delayed gastric emptying in our ovarian cancer patients after CRS-HIPEC included symptomatic therapy and supplementation with electrolytes,
Table 2 Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy characteristics (n = 77)

| Characteristic                                      | Value                           |
|-----------------------------------------------------|---------------------------------|
| Operation time (minute, median and range)           | 630 (280-960)                   |
| Intraoperative hemorrhage (mL, median and range)    | 600 (50-5000)                   |
| Number of organs resected (median and range)        | 2 (0-9)                         |
| Resected organs, n (%)                              |                                 |
| Ascending colon                                     | 18 (23)                         |
| Transverse colon                                    | 4 (5)                           |
| Descending colon                                    | 5 (6)                           |
| Sigmoid colon                                       | 19 (25)                         |
| Total colon                                          | 3 (4)                           |
| Stomach (partial)                                   | 3 (4)                           |
| Small intestine (partial)                           | 13 (17)                         |
| Rectum                                              | 46 (60)                         |
| Liver (partial)                                     | 3 (4)                           |
| Spleen                                              | 7 (9)                           |
| Pancreas (partial)                                  | 1 (1)                           |
| Gallbladder                                         | 8 (10)                          |
| Omentectomy, n (%)                                  | 56 (73)                         |
| Urinary bladder, n (%)                              | 2 (3)                           |
| Number of bowel resection, n (%)                    | 53 (69)                         |
| PCI (median and range)                              | 16 (1-39)                       |
| CCS, n (%)                                          |                                 |
| CC 0-1                                              | 60 (78)                         |
| CC 2-3                                              | 17 (22)                         |
| Chemotherapeutic agent, n (%)                       |                                 |
| Docetaxel                                           | 4 (5)                           |
| Docetaxel + carboplatin                             | 55 (71)                         |
| Mitomycin + docetaxel                               | 4 (5)                           |
| Mitomycin + carboplatin                             | 14 (19)                         |

CC: Cytoreduction; CCS: Cytoreduction scoring; PCI: Peritoneal cancer index.

minerals, proteins, and calories to maintain water and electrolyte balance and reduce malnutrition. Common symptomatic medications were antiemetic drugs, such as ondansetron, vitamin B6, and promethazine. The specific dosage depended on the patient’s age, weight and severity of DGE. Motility drugs were not used.

The limitations in the present study need to be addressed. First, this is a retrospective study with a relatively limited sample size, and an RCT study with large samples is needed to further confirm the risk factors for DGE and its effects on improved prognosis. Second, fundamental studies are needed to illustrate the potential mechanisms.

In conclusion, strengthened intestinal management, including prolonged nasogastric intubation, the use of gastrointestinal motility drugs and enteral nutrition, should be applied to patients aged ≥ 70 years or with intraoperative hemorrhage ≥ 800 mL when undergoing CRS-HIPEC.
### Table 3 Univariate analysis of risk factors associated with delayed gastric emptying after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

| Variable                                    | n  | DGE Yes | DGE No | $\chi^2$ | P value |
|---------------------------------------------|----|---------|--------|----------|---------|
| Age (yr)                                    |    |         |        |          |         |
| ≥ 70                                        | 9  | 6       | 3      | 2.697    | 0.101   |
| < 70                                        | 68 | 22      | 46     |          |         |
| BMI (kg/m²)                                 |    |         |        |          |         |
| ≥ 23                                        | 35 | 8       | 27     | 5.059    | 0.025   |
| < 23                                        | 42 | 20      | 22     |          |         |
| Pelvic surgery history                      |    |         |        |          |         |
| Yes                                         | 62 | 19      | 43     | 4.498    | 0.034   |
| No                                          | 15 | 9       | 6      |          |         |
| Comorbidity (DM/HBP)                        |    |         |        |          |         |
| Yes                                         | 24 | 12      | 12     | 2.802    | 0.094   |
| No                                          | 53 | 16      | 37     |          |         |
| History of chemotherapy                     |    |         |        |          |         |
| ≥ 7 cycles                                  | 34 | 8       | 26     | 4.334    | 0.037   |
| < 7 cycles                                  | 43 | 20      | 23     |          |         |
| CA-125 level                                |    |         |        |          |         |
| Normal (< 35 U/mL)                          | 12 | 2       | 10     | 0.990    | 0.320   |
| Elevated (≥ 35 U/mL)                        | 65 | 25      | 40     |          |         |
| Pleural effusion before surgery             |    |         |        |          |         |
| Yes                                         | 19 | 8       | 11     | 0.359    | 0.549   |
| No                                          | 58 | 20      | 38     |          |         |
| PCI                                         |    |         |        |          |         |
| ≥ 10                                        | 52 | 22      | 30     | 1.967    | 0.161   |
| < 10                                        | 14 | 2       | 12     |          |         |
| Diaphragmatic invasion                      |    |         |        |          |         |
| Yes                                         | 23 | 10      | 13     | 0.717    | 0.397   |
| No                                          | 54 | 18      | 36     |          |         |
| Perigastric and gastric dissection          |    |         |        |          |         |
| Yes                                         | 13 | 6       | 7      | 0.648    | 0.421   |
| No                                          | 64 | 22      | 42     |          |         |
| Operation time                              |    |         |        |          |         |
| ≥ 7 h                                       | 65 | 27      | 38     | 4.827    | 0.047   |
| < 7 h                                       | 12 | 1       | 11     |          |         |
| Intraoperative hemorrhage                   |    |         |        |          |         |
| ≥ 800 mL                                    | 29 | 16      | 13     | 7.112    | 0.008   |
| < 800 mL                                    | 48 | 12      | 36     |          |         |
| Anastomosis                                 |    |         |        |          |         |
| Yes                                         | 53 | 23      | 30     | 3.634    | 0.057   |
| No                                          | 24 | 5       | 19     |          |         |
Table 4 Multivariate analysis of risk factors associated with delayed gastric emptying after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

| Variable                          | OR  | 95% Confidence interval | P value |
|----------------------------------|-----|-------------------------|---------|
|                                  |     | Lower                   | Upper   |         |
| Age (yr)                         |     |                         |         |         |
| ≥ 70                             | 7.127 | 1.122                   | 45.264  | 0.037   |
| < 70                             | 1    |                         |         |         |
| Intraoperative hemorrhage        |     |                         |         |         |
| ≥ 800 mL.                        | 3.416 | 1.067                   | 10.939  | 0.039   |
| < 800 mL.                        | 1    |                         |         |         |
| BMI (kg/m²)                      |     |                         |         |         |
| ≥ 23                             | 0.450 | 0.147                   | 1.379   | 0.162   |
| < 23                             | 1    |                         |         |         |
| Operation time                   |     |                         |         |         |
| ≥ 7 h                            | 3.206 | 0.329                   | 31.226  | 0.316   |
| < 7 h                            | 1    |                         |         |         |
| History of abdominal surgery     |     |                         |         |         |
| Yes                              | 0.787 | 0.175                   | 3.538   | 0.755   |
| No                               | 1    |                         |         |         |
| History of chemotherapy          |     |                         |         |         |
| ≥ 7 cycles                       | 0.301 | 0.078                   | 1.167   | 0.082   |
| < 7 cycles                       | 1    |                         |         |         |

BMI: Body mass index.

CONCLUSION

In conclusion, strengthened intestinal management, including prolonged nasogastric intubation, using gastrointestinal motility drugs and enteral nutrition, should be applied to patients aged ≥ 70 years or with intraoperative hemorrhage ≥ 800 mL when undergoing CRS-HIPEC.

ARTICLE HIGHLIGHTS

Research background

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS-HIPEC) are alternatives for ovarian cancer. Delayed gastric emptying (DGE), a common complication of this procedure, can cause discomfort and decrease quality of life.
postoperatively. However, little attention has been given to this complication.

Research motivation

Though not life-threatening, DGE can increase the duration of postoperative hospitalization, decrease quality of life, and even affect the long-term prognosis of patients after CRS-HIPEC. More research is needed to elucidate the pathophysiology, etiology and treatment of DGE.

Research objectives

The aim of this study was to identify the risk factors for DGE in patients with ovarian cancer treated with CRS-HIPEC. Identifying patients at increased risk for DGE may aid patient selection as well as postoperative gastrointestinal management.

Research methods

A retrospective study was conducted, and risk factors for DGE were analyzed using univariate and multivariate analyses.

Research results

Age ≥ 70 years and intraoperative hemorrhage ≥ 800 mL were independently associated with postoperative DGE after CRS-HIPEC. Perigastric and gastric dissection is known to be the greatest risk factor for DGE. However, it was not found to be related to DGE in our study. The possible reason may be that the sample size was too small.

Research conclusions

Postoperative gastrointestinal management, including prolonged nasogastric intubation, should be strengthened for patients over 70 years or with intraoperative bleeding exceeding 800 mL.

Research perspectives

Large-sample RCTs are needed to further identify the risk factors and management of DGE.

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