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**Development and future perspectives of natural orifice specimen extraction surgery
for gastric cancer**

Zhang ZC *et al.* NOSES for GC

Abstract

In recent years, natural orifice specimen extraction surgery (NOSES), a novel minimally invasive surgical technique, has become a focus in the surgical field, and has been initially applied in gastric surgery in many national medical centers worldwide. In addition, this new surgical technique was launched in major hospitals in China. With an increasing number of patients who have accepted this new surgical technique, NOSES has provided new prospects for the treatment of gastric cancer (GC), which may achieve a better outcome for both patients and surgeons. More and more experts and scholars from different countries and regions are currently paying close attention to NOSES for the treatment of GC. However, there are only a few reports of its use in GC. This review focuses on the research progress in NOSES for radical gastrectomy in recent years. We also discuss the challenges and prospects of NOSES in clinical practice.

Key Words: Gastrectomy; Gastric cancer; Laparoscopic surgery; Minimally invasive surgery; Natural orifice specimen extraction surgery; Radical gastrectomy

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Core Tip: Gastric cancer (GC) is a very common malignancy worldwide. Natural orifice specimen extraction surgery (NOSES), an emerging minimally invasive surgical technique, has gradually become a new modality for the treatment of GC. NOSES has gained more and more attention as well as recognition from experts and scholars nationally and internationally. We herein discuss the research progress and application prospects of NOSES.

INTRODUCTION

Gastric cancer (GC) is a very common malignancy worldwide. It is reported that the incidence rate of GC ranks fourth in the world and is the second most common cause of cancer-related death^[1]. GC has been a focus of research in the field of gastrointestinal tumor surgery, as surgery is considered to be the most important part of GC treatment plans, especially in advanced GC. With the rapid development of surgical techniques, minimally invasive surgery has played an important role in the development of surgery. In 1994, Kitano *et al*^[2] performed laparoscopic distal gastrectomy for early GC for the first time. Thereafter, with the development of laparoscopic surgical techniques over the next 20 years, treatment for GC has gone through a series of stages from laparotomy to laparoscopy, porous laparoscopic surgery (mostly five holes) and single hole laparoscopic surgery^[3-5]. In terms of minimally invasive surgery and aesthetics, natural orifice specimen extraction surgery (NOSES) has the advantages of combined traditional laparoscopic techniques and minimally invasive surgery, including minimal cutaneous trauma and post-operative pain, fast post-operative recovery, short hospital stay, and a positive psychological impact^[6]. Technical innovation of NOSES has resulted in better treatments for patients.

It is worth mentioning that all the natural orifice transluminal endoscopic surgery (NOTES) procedures are performed through a natural cavity, without any visible scars on the surface of the body. The abdominal incision is completely eliminated as it is a minimally invasive surgical technique. However, it is difficult to perform this surgical technique using current medical technology^[6,7]. It requires surgeons to be skilled in laparoscopic techniques, especially in laparoscopic reconstruction of the digestive tract. For this reason, NOTES is carried out on a relatively modest scale.

NOSES makes full use of the latest laparoscopic instruments and techniques, and specimen extraction is achieved by taking specimens from a natural cavity (mouth, rectum, vagina) of the human body, followed by complete reconstruction of the digestive tract. This avoids abdominal incision for specimen extraction. Technically, it is easily performed by skilled surgeons. NOSES is a bridge between conventional laparoscopic surgery and NOTES^[8]. Compared with traditional laparoscopic surgery,

the minimally invasive effect of NOSES is much more significant, and postoperative recovery is faster^[9,10]. It can eliminate the risk of abdominal incision-related complications, relieve pain and achieve a better abdominal cosmetic effect.

CURRENT SITUATION OF NOSES

NOSES can complete various conventional surgical techniques (resection and reconstruction) in the abdomen and pelvis using laparoscopic instruments, robots, transanal endoscopic micro surgery or soft endoscopy and other equipment platforms. Specimens are extracted from a natural cavity (rectum, vagina or oral cavity) (Figure 1)^[6]. This is an emerging minimally invasive surgery without an abdominal incision^[6]. NOTES is a type of NOSES. In the early 1990s, a few cases with specimen extraction through a natural cavity were reported^[11,12]. In 2008, the first attempt of transvaginal specimen extraction during laparoscopic colorectal cancer surgery in 7 female patients was carried out by Palanivelu *et al*^[13], which resulted in a new era of minimally invasive gastrointestinal surgery. In 2011, Wang *et al*^[14] reported 2 female patients who underwent radical resection of rectal cancer using the transvaginal approach. There were no visible scars on the abdomen or incision-related complications. This is the first report of the operation and specimen extraction performed *via* vaginal approach in China. In 2012, the robot platform was used in the radical resection of rectal cancer for the first time in China, and specimen extraction was also performed through a natural cavity (anus)^[15]. Over the next few years, NOSES gained more interest from Chinese experts and scholars. This new surgical technique was also performed in major hospitals in China. There are now increasing numbers of related reports and patients undergoing this operation. Tang *et al*^[16] found that the NOSES group had advantages in terms of reducing postoperative complications and postoperative pain, faster recovery of gastrointestinal function and shorter postoperative hospital stay. Most notably, the physical function, role function, emotional function and overall health status in the NOSES group were significantly better than those in the conventional laparoscopic surgery group. In addition, body image scores were significantly higher in the NOSES

group. However, ⁵ there was no significant difference in long-term survival between the two groups. This operation may lead to the leakage of digestive fluid, abdominal infection, as well as local, rectal and vaginal incision recurrence^[17-20].

RESEARCH PROGRESS AND APPLICATION PROSPECTS OF NOSES IN GC

In 2011, Jeong *et al*^[21] began to apply NOSES in early GC. Following traditional laparoscopic subtotal gastrectomy with regional lymph node dissection, a posterior colpotomy was performed by an experienced gynecologist, who placed the specimen retrieval bag in the abdominal cavity. The specimen and the retrieval bag were then removed *via* the transvaginal route. The authors pointed out that this new surgical method may be feasible and safe for elderly female patients with early GC. In 2015, a 72-year-old female patient underwent total ³ laparoscopic subtotal gastrectomy, regional lymph node dissection and Roux-en-Y gastrojejunostomy^[22]. Similarly, the specimen was extracted through the colpotomy incision. In this case, the diameter of the adenocarcinoma located in the gastric antrum was only 2 cm, thus the extraction was not difficult. Postoperative histopathology of the adenocarcinoma was pT3pN0. During the next 10 mo, the patient received conventional adjuvant chemoradiotherapy, with no postoperative complications. This is the first time that transvaginal extraction was used for an advanced gastric tumor after total laparoscopic gastrectomy. This study demonstrated that NOSES is a safe and feasible procedure for advanced GC. In 2015, the World Journal of Gastroenterology reported for the first time, the application of robotic gastrectomy in 8 female patients (aged between 42 and 69 years) using the Da Vinci Robotic System, and transvaginal specimen extraction. The patients were divided into two groups according to the location of the tumor, 2 cases received robotic total gastrectomy and 6 underwent robotic distal gastrectomy, with transvaginal specimen extraction in both groups using the same method^[23]. The mean total operation time was 224 min, and the mean postoperative stay was 3.6 d. Postoperative gastrointestinal stenosis, anastomotic leakage and re-admission were not reported during the follow-up period. To some extent, this study proved the feasibility and safety of robotic radical

gastrectomy with transvaginal specimen extraction for female patients with GC. Liu *et al*^[24] reported a case of early gastric angular adenocarcinoma (cT1bN0M0). After total laparoscopic distal gastrectomy and a modified delta-shaped anastomosis, the specimen was extracted from the anus *via* the anterior rectal wall incision. During this procedure, the rectum was disinfected with iodine water, and iodophor gauze was placed in the anus for full dilation. A 6 cm incision was made on the anterior wall of the upper rectum. The specimen in the retrieval bag was slowly pulled out of the abdominal cavity through the anus to complete the extraction process. After the operation, the patient's vital signs were stable and there were no complications. The patient recovered and was discharged from hospital after 14 d. In December of the same year, Sun *et al*^[25] reported on NOSES gastrectomy in a 64-year-old male patient. After laparoscopic distal gastrectomy, the surgeon placed the retrieval bag in the abdominal cavity to retrieve the specimen, and then performed a modified gastroduodenal triangle anastomosis to complete the reconstruction of the digestive tract. The anorectum was repeatedly rinsed with iodine water, and the anorectal intestinal wall was supported by iodophor gauze after sufficient anal dilation. A 4 cm incision was made in the upper rectum, and an oval clamp was inserted through the anorectum, the specimen bag was pulled out from the incision through the anorectum to complete the removal of the surgical specimens. On the tenth day, the patient recovered and was discharged without any complications or tumor recurrence. Wang *et al*^[26] performed both total laparoscopic subtotal gastrectomy and radical anterior resection in a 65-year-old male, and the extraction of specimens was completed through the anus. The postoperative pathology confirmed that both tumors were moderately differentiated adenocarcinoma, and the lymph node in each specimen was negative. After six cycles of adjuvant chemotherapy, no recurrence was observed during the follow-up period.

The number of patients in the above case reports on GC-NOSES is limited. However, it is the only way for the NOSES technique to become popular in central hospitals and the use of this technique is only beginning. If the surgeon masters this new technique, a

stable surgical team can be established. A single center clinical study on GC-NOSES has been launched in recent years.

In 2017, Hüscher *et al*^[27] conducted a prospective, non-randomized single center clinical study of laparoscopic NOSES radical gastrectomy, which is only performed in patients with early GC. After laparoscopic gastrectomy, a 3 cm incision was made on the gastric stump. The specimen was then cut into three small segments, and stitched one by one. Finally, the specimens were removed through the oral cavity. A total of 14 patients with early GC were included in this study and they were followed up for 18 months. One patient died of postoperative pneumonia (mortality 7.14%), and the remaining patients had no serious complications or wound infection. The mean postoperative hospital stay was 4.7 ± 1.0 d. To some extent, this study indicated that the safety and feasibility of NOSES radical gastrectomy for early GC were similar to those of traditional laparoscopic surgery, but the NOSES technique did reduce the mortality and postoperative hospital stay. In the same year, a retrospective study was reported in *Polski Przegląd Chirurgiczny*, which included 50 patients with gastrointestinal stromal tumors^[28]. In this study, 12 patients' specimens were retrieved through the oral cavity and the remaining 38 via a conventional abdominal incision. The statistical results of 12 patients showed that the mean operation time was 92.5 min, the tumor size ranged from 14 mm to 40 mm, and the mean length of hospital stay was 3.2 d. Postoperative pathology confirmed that all the cases showed radical excision. One patient developed a surgical site infection and one patient had fluid collection at the suture site which prolonged hospital stay to 8 d. Following a comparative analysis, the researchers believe that the NOSES technique is a promising, safe and effective minimally invasive surgery. Recently, Wang^[29] used a type of NOSES to perform Roux-en-Y reconstruction after laparoscopic total gastrectomy with two circular staplers (one of which was oval). The advantage of this technique is that it can be applied to the tumor located very close to the cardia. Thus, it could obtain a high-quality anastomosis effect, and a laparoscopic suture is not required to close the intestinal common opening. Consequently, the

operation time could be significantly shortened and the patient's gastrointestinal function would recover more quickly.

NOSES, a new surgical technique, is now carried out in more and more hospitals. However, there is still a lack of standardization in this novel minimally invasive surgery. In June 2017, Professor Wang Xi-Shan and other experts initiated the China NOSES Alliance and the NOSES Special Committee of Colorectal Surgeons Branch of Chinese Medical Doctor Association. In 2019, the NOSES Special Committee issued the International Consensus on NOSES for GC^[30]. The consensus systematically named and standardized the NOSES procedure for GC. According to three factors related to the resection range, as well as the type of digestive reconstruction and specimen extraction route, the method of NOSES for GC can be divided into nine types (Table 1)^[6]. In addition, the consensus described in detail the indications and contraindications, precautions and approach of surgery, and solutions to the difficulties in specimen extraction of GC-NOSES, which would be instructive for the development of NOSES in clinical practice. In general, there are seven steps in the NOSES procedure: (1) Preoperative course; (2) Positioning and placement of trocars; (3) Localization of the tumor; (4) Laparoscopic subtotal gastrectomy; (5) Trans-natural cavity (mouth, rectum, vagina) specimen extraction; (6) Digestive tract reconstruction; and (7) Postoperative course. More significantly, the resection range of gastrectomy cannot be intentionally reduced due to specimen extraction through a narrow orifice. Based on different tumor locations, the methods of gastrectomy and reconstruction should be carefully selected to preserve gastrointestinal function. In addition, the anastomosis should be provided with a sufficient blood supply, no tension or stenosis^[31].

CONCLUSION

NOSES is better than traditional laparoscopic assisted radical gastrectomy for GC in some aspects. For example, it avoids abdominal surgical incision, and eliminates incision-related complications such as incision site infection, difficult or non-healing incision, wound dehiscence, incisional hernia, abdominal incision tumor implantation,

and even the pain and scarring caused by the incision^[32]. In addition, it can eliminate the incision scar related psychological impact, psychological burden and psychological trauma of surgery^[8]. NOSES for GC also reflects the doctor's pursuit of people-oriented principle, by prioritizing the interests of the patients. However, we should also pay attention to the shortcomings and potential complications of NOSES for GC. For example, due to the unique intraluminal anastomosis and the approach of specimen extraction in NOSES for GC, there are potential risks, such as intraperitoneal exposure and dissemination of tumor cells, intraperitoneal bacterial infection, structural or functional damage of natural lumen, abscission and implantation of tumor cells. Due to the lack of relevant reports on NOSES for GC, we can only learn from other literature reports on gastrointestinal surgery using this technique.

In recent years, specimen extraction *via* a natural orifice, an emerging minimally invasive surgical technique, has become one of the research hotspots in the surgical field nationally and internationally. This technique has been preliminarily applied to gastroenterological surgery in many national medical centers around the world. With the increasing number of surgical cases, NOSES has gradually become a novel modality for GC treatment, which not only provides a better treatment choice for patients and operators, but has also gained more and more attention and recognition from experts and scholars worldwide.

However, we should also be aware that the clinical development of GC-NOSES is still in its infancy. Research on GC-NOSES has mainly focused on single-center, small sample and retrospective analyses^[22,23], indicating a lack of large sample and multi-center prospective studies to support the extensive development of GC-NOSES in evidence-based medicine. In addition, GC-NOSES related complications deserve further investigation, such as abdominal infection, natural orifice injury, tumor implantation metastasis, anastomotic leakage, prognosis and recurrence in patients, and its long-term efficacy.

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