Original Article

Short-term clinical effects and inflammatory response of natural orifice specimen extraction surgery versus conventional laparoscopic-assisted surgery for the treatment of sigmoid and rectal cancer

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Background: The clinical outcomes and benefits of natural orifice specimen extraction surgery (NOSES) in colorectal cancer have not been fully evaluated comparing to conventional laparoscopic-assisted radical resection. This retrospective study was conducted to investigate the short-term clinical benefits of NOSES versus conventional laparoscopic-assisted surgery for the treatment of sigmoid and rectal cancer.

Methods: A total of 112 patients with sigmoid or rectal cancer were included in this retrospective study. The observation group (n=60) was treated with NOSES, and the control group (n=52) was treated with conventional laparoscopic-assisted radical resection. Following these interventions, the postoperative recovery and inflammatory response indexes were compared between the two groups.

Results: In contrast with the control group, the observation group significantly had longer operation time (t=2.83, P=0.006), but shorter durations for the resumption of a semi-liquid diet (t=2.17, P=0.032), and length of postoperative hospital stay (t=2.74, P=0.007), as well as fewer postoperative incision infections (χ^2=7.32, P=0.009). Moreover, the levels of immunoglobulin (Ig), including IgG (t=2.29, P=0.024), IgA (t=3.30, P=0.001), and IgM (t=3.38, P=0.001), in the observation group were markedly higher than those within the control group at 3 days postoperatively. Also, the levels of inflammatory indicators including interleukin (IL)-6 (t=4.22, P=5.02E–5), C-reactive protein (CRP) (t=3.73, P=3.5E–4), and tumor necrosis factor (TNF)-α (t=2.94, P=0.004) in the observation group were considerably lower than those in the control group at 3 days after the operation.

Conclusions: NOSES can improve the postoperative recovery and has benefits in reducing the inflammatory response than conventional laparoscopic-assisted surgery.

Keywords: Natural orifice specimen extraction surgery (NOSES); conventional laparoscopic-assisted surgery; colorectal cancer; short-term clinical effects; inflammatory response

Introduction

At present, surgery is the main treatment for colorectal cancer. Compared to the open surgery, the laparoscopic surgical approach has been broadly used owing to its advantages in terms of rapid recovery, less intraoperative blood loss and postoperative complications (1). The conventional laparoscopic-assisted radical resection of colorectal cancer is required an auxiliary incision in the abdominal wall for anastomosis and reconstruction of the digestive tract. With the improvement of minimally invasive technology, the emergence of NOSES provides a new method for the treatment of colorectal cancer, including sigmoid and rectal cancer. This operation utilizes a laparoscopic approach for intracorporeal anastomosis without auxiliary incision, by completing the reconstruction of the digestive tract *in vivo*, which has the advantages of smaller wounds and less invasiveness (2,3). However, the clinical outcomes and benefits of NOSES in sigmoid and rectal cancer have not been fully evaluated. It has been hypothesized that the immunologic response might be related to the surgical outcomes, as the postoperative immune response not only responds to postoperative infection but also to tumor spread and metastases (4-6). This retrospective study was conducted to investigate the

short-term clinical benefits of NOSES versus conventional laparoscopic-assisted surgery for the treatment of sigmoid and rectal cancer. The postoperative clinical outcomes and inflammatory responses were used to reflect the short-term clinical effects and the potential recovery ability, respectively. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-23-144/rc).

Methods

Participants

A total of 112 patients with sigmoid and rectal cancer admitted to Affiliated Hospital of Guangdong Medical University from February 2019 to April 2022 were included, with 60 cases in the observation group and 52 cases in the control group. All participants underwent a series of evaluations. The inclusion criteria were as follows: (I) tumors located in sigmoid or upper rectum, and those less than 5 cm, as determined by preoperative radiologic examination; (II) patients diagnosed with colorectal cancer according to the pathological criteria; (III) cases consistent the indications for surgical treatment and without contraindications; (IV) non-emergency surgery; and (V) without perforation, bleeding, obstruction pelvic infection, or anorectal disease.

Patients were excluded based on the following criteria: (I) serious dysfunction of the heart, kidneys, or other organs; (II) multiple primary tumors; (III) imaging evidence of local invasion and metastatic cancer; (IV) previous surgical treatment of colorectal cancer; (V) estimated survival time <6 months; (VI) history of abdominal, pelvic, and anorectal surgery; (VII) patients with autoimmune or infectious diseases and (VIII) have preoperative steroid use. This study conformed to the provisions of the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the ethics committee of the Affiliated Hospital of Guangdong Medical University (Registration No. PJ2020-090) and informed consent was taken from all the patients.

Surgical procedure

The surgical procedure was performed under general anesthesia in a sterilized operating area and with sterile clothing. A five-hole method was employed to place the abdominal wall puncture devices. Tumor dissociation and dissection of lymphoid tissue were conducted according


Highlight box

Key findings
• Natural orifice specimen extraction surgery effectively decreases the duration for the resumption to semi-liquid diet, and length of postoperative hospital stay. Furthermore, it also has fewer postoperative incision infections and causes significantly less impairment of the immune system compared to conventional laparoscopic-assisted surgery.

What is known and what is new?
• Natural orifice specimen extraction surgery has the advantages of smaller wounds and less invasiveness but its clinical benefits in the treatment of sigmoid and rectal cancer still need to be evaluated.
• This study investigated the postoperative clinical outcomes and inflammatory response of natural orifice specimen extraction surgery versus conventional laparoscopic-assisted surgery in the treatment of sigmoid and rectal cancer.

What are the implications, and what should change now?
• Natural orifice specimen extraction surgery is superior to conventional laparoscopic-assisted surgery in the treatment of sigmoid and rectal cancer because it not only has clinically significant benefits but also has fewer adverse effects on the immune system.
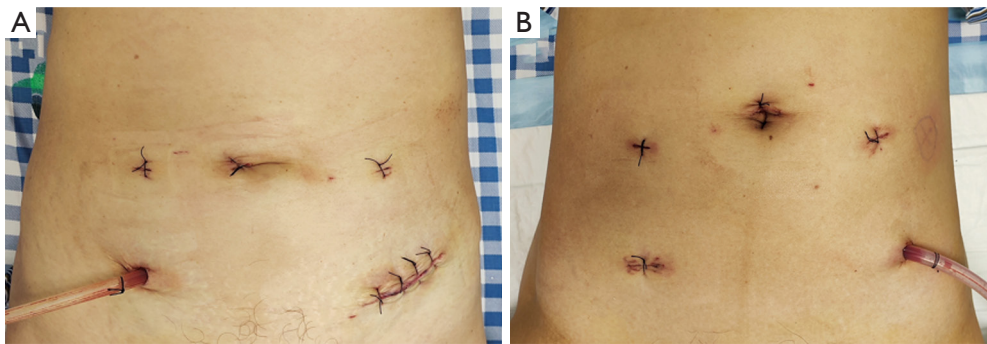
Figure 1 Representative operative incision for conventional laparoscopic-assisted surgery and natural orifice specimen extraction surgery. (A) Surgical wounds from conventional laparoscopic-assisted surgery; (B) surgical wounds from natural orifice specimen extraction surgery.

to the laparoscopic radical sigmoidectomy or proctectomy protocol. Cefuroxime was routinely given 30 minutes before the operation and the first day after surgery. Re-dosing given was required if the operation duration exceeds 3 hours.

The control group was treated with conventional laparoscopic-assisted radical sigmoidectomy or proctectomy. A plastic wound protector was used to cover the abdominal incision. After separation of the mesocolon, the proximal colon was split and placed the anvil. Then tumor tissue was removed.

The observation group was treated with CRC-NOSES VI or V. A linear cutter stapler was utilized to split proximal and distal colon of tumor. A vaginal or rectal incision was made after lavage, and then a plastic wound protector was used to put the anvil into enterocoelia and remove the excised diseased tissue. Next, the anvil was introduced into the proximal colon. The open rectal or vaginal stump was closed with a linear stapler.

In the two groups, the circular stapling device was introduced into the rectum, and an end-to-end anastomosis was performed. Postoperative interventions such as anti-infection, fluid rehydration, and fasting were then carried out (*Figure 1*).

Outcomes measures

(I) Perioperative recovery evaluation (7): outcomes such as operation time, intraoperative blood loss (which was evaluated by the gauze sponges), duration for the first postoperative exhaust, duration for the first postoperative defecation, duration for resumption of a semi-liquid diet, length of hospital stay, and postoperative complications were included in the evaluation. (II) T lymphocyte subsets

indicators (8), including $CD3^+$, $CD4^+$, $CD8^+$, and $CD4^+/CD8^+$ were observed. Next, 5 mL of fasting peripheral venous blood was extracted, detected using an EPICSXL flow cytometer (BECKMAN COULTER, USA), and the $CD4^+/CD8^+$ ratio was calculated. (III) Immunoglobulin levels (9), including immunoglobulin G, M, and A (IgG, IgM, and IgA) were also observed. 5 mL of fasting venous blood was extracted, placed at room temperature for 1 h, and then centrifuged to separate serum. Subsequently, immune turbidimetry detection was utilized in the analysis (4). C-reactive protein (CRP) was detected by radioimmunoassay, and interleukin (IL)-6 and tumor necrosis factor (TNF)-α were detected by enzyme-linked immunosorbent assay (10). All peripheral venous blood samples were obtained 1 day preoperatively and 3 days postoperatively.

Statistical methods

Statistical analysis and graphs were performed and generated using R version 3.6.2. [R Core Team *(2022)*. R Foundation for Statistical Computing, Vienna, Austria]. Quantitative variables were analyzed using the Student's *t*-test and were expressed as the mean ± standard deviation (SD). Categorical variables were expressed as a percentage (%) and were contrasted by using Pearson's Chi-Square (χ^2) test or Fisher's exact test as appropriate. $P<0.05$ was considered to indicate statistical significance.

Results

The clinical characteristic of the participants

The observation group comprised a total of 35 males and 25

Table 1 The clinical characteristics of patients in the observation and control groups

Clinical characteristics	Control group (n=52)	Observation group (n=60)	t/χ^2	P
Age (years), mean ± SD	62.77±11.38	59.75±11.82	1.37	0.173
Gender, n (%)			0.12	0.730
Male	32 (61.54)	35 (58.33)		
Female	20 (38.46)	25 (41.67)		
BMI (kg/m^2), mean ± SD	23.05±2.86	23.35±2.30	0.63	0.520
Tumor size (mm), mean ± SD	27.90 ± 5.82	28.89 ± 5.43	0.92	0.360
pTNM stages, n (%)			1.55	0.908
I	20 (38.46)	24 (40.00)		
IIA	11 (21.15)	14 (23.33)		
IIB	4 (7.69)	2 (3.33)		
IIIA	3 (5.77)	2 (3.33)		
IIIB	9 (17.31)	12 (20.00)		
IIIC	5 (9.62)	6 (10.00)		

SD, standard deviation; BMI, body mass index; TNM, tumor, node, metastasis staging.

females, with 59.75±11.82 years. Also, there were 32 males and 20 females in the control group, with 62.77±11.38 years. The differences in the clinical characteristics between observation and control groups, including age, gender, BMI, duration, and distribution of tumor, tumor size, node, metastasis (TNM) stages were not statistically significant (P>0.05, *Table 1*).

Perioperative outcomes

Compared to the conventional laparoscopic-assisted surgery, significant differences were observed in the effect of NOSES on the duration for the operation time (t=2.83, P=0.006), duration for the resumption of a semi-liquid diet (t=2.17, P=0.032), length of postoperative hospital stay (t=2.74, P=0.007), and postoperative incision infection (χ^2=7.32, P=0.009). However, the differences between the groups in terms of the perioperative outcomes of intraoperative blood loss (t=1.26, P=0.209), duration for the first postoperative exhaust (t=1.73, P=0.086), duration for the first postoperative defecation (t = 0.99, P=0.320), and postoperative complications including anastomotic leakage (χ^2=0.02, P=0.884) are not significant, as shown in *Table 2*.

Postoperative inflammatory response

No remarkable differences were observed in the T

lymphocyte subset indicators, including CD3$^+$ (t=0.74, P=0.463), CD4$^+$ (t=0.12, P=0.908), CD8$^+$ (t=0.06, P=0.950), and CD4$^+$/CD8$^+$ ratio (t=0.39, P=0.698) between the observation and control group at 3 days postoperatively (as shown in *Figure 2*, *Table 3*). The levels of IgG (t=2.29, P=0.024), IgA (t=3.30, P=0.001), and IgM (t=3.38, P=0.001) in the observation group were significantly higher than those in the control group at 3 days after the operation (*Figure 3*, *Table 3*). Moreover, the levels of IL-6 (t=4.22, P=5.02E–5), CRP (t=3.73, P=3.5E–4), and TNF-α (t=2.94, P=0.004) in the observation group were significantly lower than those in the control group at 3 days post-surgery (*Figure 4*, *Table 3*). There were no significant differences in all indicators between the two clusters preoperatively (P>0.05) (*Table 3*).

Discussion

In conventional laparoscopic-assisted surgery, an auxiliary incision in the abdominal wall is required for anastomosis, which will easily cause scarring and also increase the occurrence of complications such as postoperative incision infection (11-14). In NOSES, the resection and separation of tumor tissue and anastomosis are completed intraoperatively in the abdomen. The resected tumor tissue does not need to be taken out through the auxiliary incision but is removed through a natural orifice (anus, vagina, etc.) (15).

Table 2 Comparison of the perioperative outcomes between the observation and control groups

Perioperative outcomes	Control group	Observation group	t/χ^2	P
Operation time (min)	165.40±49.58	195.72±62.10	2.83	0.006
Intraoperative blood loss (mL)	42.12±19.84	47.67±25.74	1.26	0.209
Duration for the first postoperative exhaust (days)	2.85±1.59	2.33±1.57	1.73	0.086
Duration for the first postoperative defecation (days)	3.83±1.89	3.48±1.84	0.99	0.320
Duration for resumption of a semi-liquid diet (days)	4.86±2.05	4.02±2.07	2.17	0.032
Length of postoperative stay in hospital (days)	9.89±4.48	7.80±3.61	2.74	0.007
Postoperative complications				
Incision infection	6 (11.54)	0 (0.00)	7.32	0.009
Anastomotic leakage	2 (3.85)	2 (3.33)	0.02	0.884

Data are shown as mean ± SD or n (%).
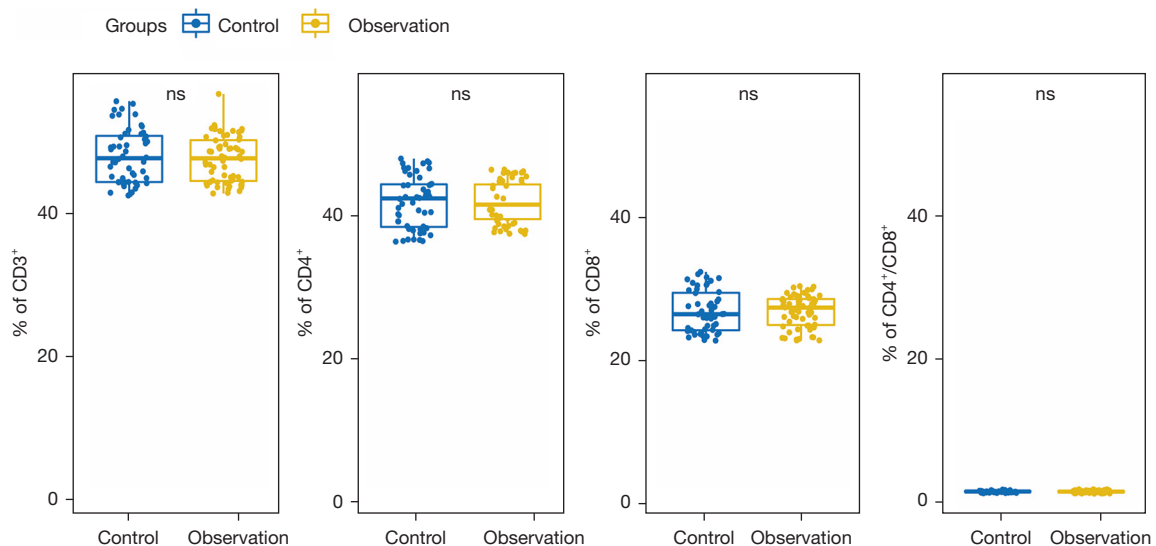
Figure 2 Comparison of the T lymphocyte subsets between the observation and control groups. ns, not significant.

Compared to conventional laparoscopic-assisted surgery, the greatest advantage of NOSES is that it effectively reduces postoperative scar formation while reducing complications caused by the incision (16-18). Numerous articles have confirmed the advantages of NOSES. In previous studies, specimen extraction by natural orifice and abdominal incision were respectively performed in patients with colorectal cancer, and the reported results demonstrated that the first postoperative exhaust time of NOSES was markedly shorter than that of conventional laparoscopic-assisted surgery, and the postoperative complications were also decreased (19,20). In the present study, we observed notable differences in the duration for the resumption of a semi-liquid diet, length of postoperative hospital stay, and postoperative incision infection between the two groups. In summary, NOSES need a longer operation time, but could effectively decrease the duration for the resumption to semi-liquid diet, and length of postoperative hospital stay. Our results highlighted the benefits of NOSES for the treatment of sigmoid and rectal cancer relative to conventional laparoscopic-assisted radical resection.

Surgery itself is an exogenous stress trauma, which will have a certain impact on the body's immune function. The damage caused by surgery to the body can also be assessed

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Table 3 Comparison of the inflammatory response between the observation and control groups

Inflammatory markers	Periods	Control group	Observation group	t	P
IL-6 (ng/L)	Preop.	22.35±2.78	22.47±3.20	0.21	0.831
	Post.	43.78±7.85	37.92±6.84	4.22	5.02E–5
CRP (mg/L)	Preop.	7.00±0.87	7.18±0.89	1.07	0.289
	Post.	26.34±6.70	22.32±4.22	3.73	3.5E–4
TNF-α (ng/L)	Preop.	36.01±1.36	36.11±1.62	0.37	0.709
	Post.	47.25±4.79	44.99±3.01	2.94	0.004
CD3$^+$	Preop.	51.80±2.91	51.75±2.96	0.08	0.936
	Post.	48.02±3.76	47.53±3.18	0.74	0.463
CD4$^+$	Preop.	27.52±3.05	26.98±2.93	0.97	0.336
	Post.	41.87±3.59	41.80±2.87	0.12	0.908
CD8$^+$	Preop.	28.07±1.29	28.28±1.35	0.82	0.416
	Post.	26.49±2.84	26.52±2.19	0.06	0.950
CD4$^+$/CD8$^+$	Preop.	0.98±0.11	0.96±0.11	1.19	0.237
	Post.	1.60±0.24	1.59±0.17	0.39	0.698
IgG (IU/mL)	Preop.	139.50±10.03	140.25±8.10	0.44	0.662
	Post.	137.79±10.36	141.70±7.65	2.29	0.024
IgA (IU/mL)	Preop.	151.62±3.09	152.35±2.74	1.32	0.190
	Post.	150.87±10.86	157.98±11.75	3.30	0.001
IgM (IU/mL)	Preop.	167.87±2.83	168.76±2.83	1.67	0.098
	Post.	153.72±15.33	163.12±14.10	3.38	0.001

Data were shown as mean ± standard deviation. IL, Interleukin; CRP, C-reactive protein; TNF, tumor necrosis factor; Ig, immunoglobulin; Preop., preoperative; Post., postoperative.
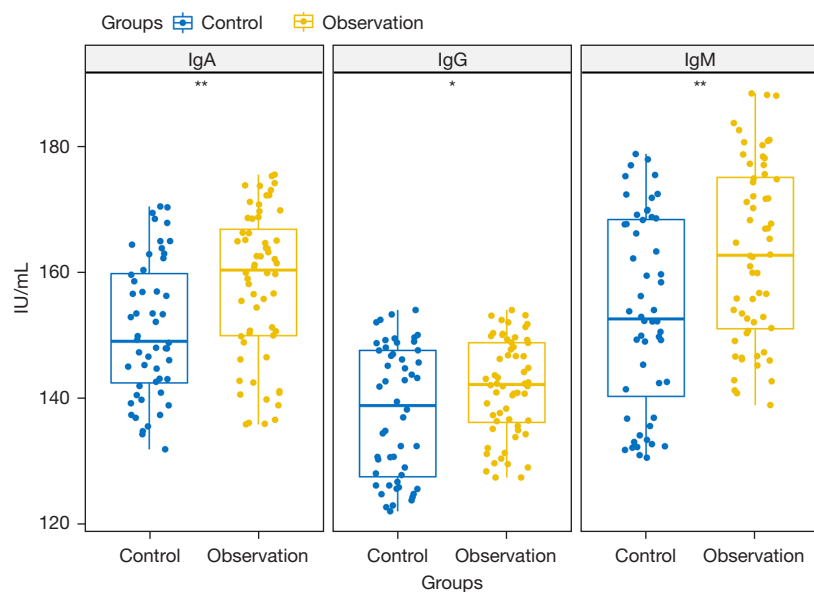
Figure 3 Comparison of the immunoglobulin levels between the observation and control groups. *, P≤0.05; **, P≤0.01. Ig, immunoglobulin.
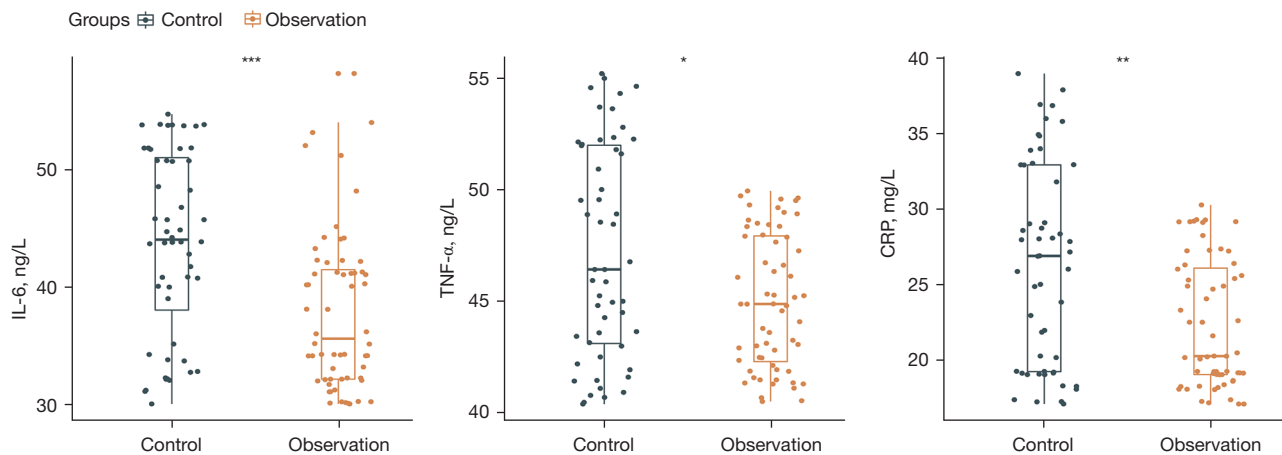
Figure 4 Comparison of the inflammatory indicators between the observation and control groups. *, P≤0.05; **, P≤0.01; ***, P≤0.001. IL, interleukin; TNF, tumor necrosis factor; CRP, C-reactive protein.

by detecting the immune function indicators of patients. Moreover, their postoperative recovery can also be reflected by the immune function indicators (21). For instance, T lymphocyte subsets, cellular immunity, and CD4+ activation can release a large number of cytokines that enhance the body's anti-tumor effect. Furthermore, CD8+ can adhere to and clear viruses (22). Serum immunoglobulin can bind to the tumor antigen and dissolve it. IgG binds macrophages and promotes their phagocytosis to fight cancer. Also, IgA can effectively protect the body mucosa and protect it from damage (23). As an inflammatory factor, CRP is a more sensitive immune indicator in the early stage. In addition, IL-6 is a pro-inflammatory factor that induces inflammatory damage; increased levels of IL-6 are related to the degree of damage and indicate that the body is stimulated or injured externally. TNF-α can be used to assess the degree of trauma by inducing cells to produce various inflammatory cytokines, such as IL-6 (24). In this study, the levels of immunoglobulin indicators were increased, and the levels of inflammatory indicators were decreased in the observation group compared to the control group. This result is consistent with the perioperative clinical outcomes. For example, the shorter duration for resumption of a semi-liquid diet induces faster recovery might be reflected by the immune function indicators. Our results showed a reduced postoperative inflammatory response with the NOSES compared to the conventional laparoscopic-assisted radical resection.

However, it should be noted that NOSES requires the surgeon to operate and master the reconstruction of

the digestive tract *in vivo*. For patients with large tumors or obesity, it is difficult in extraction of specimen from the natural orifice, especially in rectum. Therefore, a comprehensive evaluation is necessary to decide whether the patient meets the criterion of this procedure, which will facilitate the selection of the most appropriate treatment (25). And the comparison for long-term clinical outcomes of two surgical techniques needs to be evaluated in the further studies.

Conclusions

In conclusion, NOSES has clinically relevant advantages, including reducing the duration for the resumption of a semi-liquid diet, the length of postoperative hospital stay, and fewer postoperative incision infections. Moreover, it also causes less impairment of the immune system than conventional laparoscopic-assisted surgery. The findings of the present study support the hypothesis that NOSES can improve the postoperative recovery and has the benefits in reducing the inflammatory response than conventional laparoscopic-assisted surgery in sigmoid and rectal cancer.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo. amegroups.com/article/view/10.21037/jgo-23-144/rc

Data Sharing Statement: Available at https://jgo.amegroups. com/article/view/10.21037/jgo-23-144/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups. com/article/view/10.21037/jgo-23-144/coif). The authors have no conflicts of interest to declare.

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 ethics committee of the Affiliated Hospital of Guangdong Medical University (Registration No. PJ2020-090) and informed consent was taken from all the patients.

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