



Natural orifice specimen extraction surgery in left-sided colon and upper rectal cancer: a narrative review

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Background and Objective: Natural orifice specimen extraction surgery (NOSES) is an innovative technique, used in minimally invasive surgery for colorectal cancer. NOSES has been demonstrated as a safe and effective method in patients matching the inclusion criteria. Objective was to analyze and review articles regarding short- and long-term outcomes in NOSES in left-sided colon and upper rectal cancer.

Methods: We conducted a search in PubMed and Cochrane Reviews databases and reviewed the studies in English regarding NOSES in left-sided colon and upper rectal cancer published until May 2022.

Key Content and Findings: This literature review contains short summary of the recent articles' results regarding NOSES in left-sided and upper rectal colon cancer. Studies showed better short-term outcomes and comparable with conventional laparoscopy long-term outcomes. Pitfalls and challenges of NOSES-studies include implementing standardized research protocols and thoughtful recruitment of patients due to the necessity of getting accurate and reproducible results.

Conclusions: The advantages of NOSES in colorectal cancer treatment including reduction in postoperative pain and wound complications, less use of postoperative analgesics, faster recovery of bowel function have been described in left-sided colon and upper rectal cancer treatment. Oncological outcomes do not differ with conventional laparoscopic surgery with specimen extraction via laparotomy.

Keywords: Natural orifice specimen extraction surgery (NOSES); colorectal cancer; left-sided colon cancer; laparoscopic colorectal surgery

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Introduction

Nowadays minimally invasive surgery (MIS) is widespread due to better short-term outcomes in comparison to open surgical procedures. Laparoscopic colon cancer surgery (LCCS) was associated with less intraoperative blood loss,

less postoperative pain and fever, shorter use of oral and parenteral analgesics, faster recovery of bowel function and shorter time of the hospital stay (1-4). These benefits become particularly important in comorbid, elderly and fragile patients (5). Performing LCCS, surgeons regularly

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extract a specimen with a tumor via minilaparotomy. Length of the required incision is determined by tumor size and its location, and it may vary considerably. Any incision is a surgical trauma that may cause poorer short-term outcomes and limit the LCCS benefits and provide patients the best treatment results. Natural orifice specimen extraction surgery (NOSES) is used to avoid auxiliary incisions. It may decrease the rate of postoperative complications, such as wound-site infections and improve patients' quality of life after surgery. NOSES, as any surgical approach, requires patient selection, and has determined indications and contraindications. The crucial limiting factor is the size of the tumor. The required diameter of the tumor is up to 3 cm for the transanal specimen extraction and up to 5 cm for the transvaginal specimen extraction. Also, contraindications and limiting factors are based on the tumor location, the total size of the specimen and the estimated invasion depth of the neoplasm and body mass index (BMI) (6).

NOSES had been developing for the last thirty years alongside wide-spreading MIS techniques. Stewart *et al.* (7) and Nezhat (8) were the first ones who reported the retrieval of a specimen through the vagina in 2001. Shortly thereafter, Franklin *et al.* published the first clinical case of partial colectomy with NOSES via the anus (9). Palanivelu *et al.* named the non-abdominal incision surgery as NOSE in 2008 (10). In 2019, the international consensus on NOSES for colorectal cancer was formulated (11). The International Alliance of NOSES, established in 2018, created a full introduction of the theoretical and technical aspects of the procedure. Three years later, in 2021, the second edition of the English book on NOSES was published, where preoperative preparation and key technical points were described in detail (6). In this article we reviewed the short- and long-term outcomes described in recent studies regarding NOSES in splenic flexure, descending colon, sigmoid colon, upper and middle rectal tumors. This selection is based on various strong reasons. It is known that the right and left colon have separate sources of blood supply. There is superior mesenteric artery for the right colon and inferior mesenteric artery for the left colon, and, moreover, it represents embryologic origins of the midgut and hindgut (12). The cecum to the proximal two-thirds of the transverse colon derives from the midgut. The segment comprising the distal third of the transverse colon to the upper anal canal derives from the hindgut (13). Cancers of the right and left side of the colon differ in clinical and pathological features. There are histological and molecular subtypes of colon cancer that define

treatment solutions, such as required surgical procedures, chemotherapy and biological therapy regimen. Choosing NOSES type and its technical features directly depends on the location of the tumor that will be discussed below. Common options for left-sided colon and upper and middle rectum cancer (possibility of anterior resection depending on the tumor distance from the anal verge, in studies we reviewed anterior resections for upper and middle rectum cancers were merged) included colorectal cancer natural orifice specimen extraction surgery (CRC-NOSES) procedures with complete dissection and transection of specimen in abdominal cavity and its extraction via anus or vagina.

The authors' personal experience also served as the basis for some of the opinions in this article. We present the following article in accordance with the Narrative Review reporting checklist (available at <https://ales.amegroups.com/article/view/10.21037/ales-22-30/rc>).

Objective

The primary endpoint of the study was to determine the main principles, indications, contraindications, and surgical features regarding NOSES in splenic flexure, descending colon, sigmoid colon, upper and middle rectal tumors based on published data. The secondary endpoint was to evaluate the long-term outcomes after NOSES procedures for left-sided colon cancer, treated with left-sided colon resection, sigmoid colon resection, and anterior rectal resection.

Methods

Search strategy

We conducted a search of the electronic medical databases, including a comprehensive analysis of the PubMed and Cochrane databases, to identify all relevant publications regarding NOSES for left-sided colon, and upper rectal cancer. All articles, published in English-language journals until May 2022, were eligible. We thoroughly analyzed articles that fulfilled the search criteria described below in *Table 1*.

Search results

We used MeSH descriptor "colon cancer" with qualifier "surgery-SU" to conduct a search in Cochrane database. We found 3 Cochrane Reviews and 579 Cochrane Trials related to surgical colon cancer treatment. After rejecting non-

Table 1 The general search strategy summary

Items	Specification
Date of search	01/05/2020
Databases and other sources searched	PubMed, Cochrane Library
Search terms used	MeSH descriptor “colon cancer” with qualifier “surgery - SU”; PubMed query (“natural orifice specimen extraction”) [Title/Abstract] AND (“colorectal cancer”) [Title/Abstract]
Timeframe	2009–2022
Inclusion and exclusion criteria	Inclusion criteria: all study types (literature reviews, case-control and randomized controlled studies, systematic reviews and meta-analyses); Exclusion criteria: non-colon cancer and non-NOSES studies, tumor location—right-sided colon and low rectal cancer, non-English articles
Selection process	All authors

relevant reviews and trials, we found one Cochrane Trial on NOSES application in left-sided colon and upper rectal cancer. We conducted a search in PubMed by the query (“natural orifice specimen extraction”) [Title/Abstract] AND (“colorectal cancer”) [Title/Abstract]. We got 50 results. After rejecting non-relevant papers on right-sided colon and low rectal cancer, 21 studies were selected. They included literature reviews, case-control and randomized controlled studies, systematic reviews and meta-analyses.

The primary endpoint of analysis was to describe the approach to NOSES type selection depending on tumor location and surgical peculiarities.

Results

NOSES can be divided into two types based on the specimen retrieval site. There are transvaginal and transanal specimen extractions used in CRC-NOSES. Choosing NOSES type depends on size and location of the tumor. Middle rectal cancer required CRC-NOSES II with transanal specimen extraction or CRC-NOSES III with transvaginal specimen extraction. For patients with a tumor at the upper rectum, CRC-NOSES IV (with the specimen retrieval via anus) and CRC-NOSES V (the specimen retrieval via vagina) approaches are applicable. If a malignant lesion is localized in the descending colon or the proximal sigmoid colon, left colon resection can be performed via CRC-NOSES VIA (with transanal specimen extraction) or CRC-NOSES VII (with transvaginal specimen extraction). For tumors up to 3 cm in diameter localized at the splenic flexure and left transverse colon,

CRC-NOSES VIB with the transrectal specimen extraction is a possible procedure.

We summarized CRC-NOSES procedures depending on specimen retrieval site and tumor location in *Table 2*. We also provided a short summary including key CRC-NOSES features for clinicians in *Table 3*.

Short-term outcomes (operative time, blood loss, postoperative pain scores, wound complications rate, use of postoperative analgesia, recovery of bowel function, length of hospital stay) were studied in case-control studies and randomized clinical trials relating to CRC-NOSES. Researchers have also considered long-term outcomes including cosmetic and psychological effects regarding postoperative scars, rate of local recurrence and 5-year survival rate compared to conventional laparoscopic procedures. Herein, we described and discussed recent research results. We hope that this review provides clinicians information regarding NOSES benefits and limitations. Moreover, it would assist surgeons in taking decisions on implementation of CRC-NOSES in their institutions for left-sided colon cancer treatment.

Operative time and blood loss

Chang *et al.* (14) conducted a propensity score-matched study to compare patients undergoing reduced port laparoscopic surgery with natural orifice (RPLS-NOSE) or conventional (mini-laparotomy) specimen extraction (RPLS-CSE). Patients were diagnosed with sigmoid or upper rectal cancer. Compared to RPLS-conventional laparoscopy, RPLS-NOSE was associated with longer

Table 2 CRC-NOSES approaches depending on specimen retrieval site and tumor location

Type of the specimen extraction, tumor location	Transvaginal (tumor <5 cm)	Transanal (tumor <3 cm)
Middle rectal cancer	CRC-NOSES II	CRC-NOSES III
Upper rectal cancer	CRC-NOSES V	CRC-NOSES IV
Descending colon, proximal sigmoid colon	CRC-NOSES VII	CRC-NOSES VIA
Splenic flexure and left transverse colon	–	CRC-NOSES VIB

CRC-NOSES, colorectal cancer natural orifice specimen extraction surgery.

Table 3 CRC-NOSES for left-sided colon and upper rectum cancer: short summary

Features	Summary
Main procedures	Dissection and transection of specimen in the abdominal cavity Resection Specimen extraction
Indications	Tumor size: for transvaginal specimen retrieval <5 cm and for transanal <3 cm
Contraindications	The tumor is too large to be pulled out through the anus or vagina Tumor invasion beyond the serosa Obesity (BMI >36 kg/m ²)
Benefits	Less postoperative pain, faster bowel function recovery Better psychological long-term effect
Limitations & challenges	Preoperative preparation Surgery team training and experience Equipment (Ultrasonic scalpel, 60 mm linear Endo GIA stapler, 30 mm circular stapler, sterile protective sleeve)

CRC-NOSES, colorectal cancer natural orifice specimen extraction surgery; BMI, body mass index.

operative time (223.9 vs. 188.7 min; $P=0.003$). Lui *et al.* demonstrated no significant differences were observed in total operation time (145.56 vs. 142.11 min) (15). The estimated intraoperative blood loss (63.94 vs. 62.55 mL) was not significantly different between groups. In this study patients with sigmoid colon and upper rectal cancer underwent NOSES with transanal specimen extraction (50 patients) and conventional laparoscopy (75 patients). In the meta-analysis by Xu *et al.*, 10 studies were described. The operative time in the NOSES group was significantly increased compared with that in the conventional laparoscopy group [mean difference (MD) =12.38; 95% CI: 5.49 to 19.27; $I^2=72\%$; $P=0.0004$] (16).

Post-operative pain and use of analgesics

Abovementioned propensity score-matched study by Chang

et al. (14) showed that RPLS-NOSE was associated with decreased use of analgesics in comparison to conventional (mini-laparotomy) specimen extraction (morphine dose 33.9 vs. 43.4 mg; $P=0.011$). NOSES enhanced the advantages of reduced port laparoscopic surgery by avoiding the abdominal wall incision for specimen extraction in patients with tumor diameter ≤ 5 cm (14). We suggested that sample size is sufficient enough to estimate accurately short-term outcomes. This study analyzed a retrospective single-center experience, so design of the study can be considered as a limitation.

Notably, in Jong *et al.* (17) case study patients that were undergoing transrectal NOSES in left hemicolectomy (CRC-NOSES VIB) the mean pain score was 3.0 during postoperative recovery. There is a prospective study regarding left hemicolectomy (amount of evidence regarding CRC-NOSES VI is limited) with a long period of

the patients' follow-up. However, sample size is a limitation of this study (were included twenty patients). In Xu *et al.* meta-analysis (16) of six studies evaluated the pain score on the first day after surgery. The pain score is significantly lower after NOSES than conventional laparoscopy, and the difference was significant (MD = -1.83; 95% CI: -2.53 to -1.13; $I^2=90\%$; $P<0.00001$). Four studies recorded the analgesics use. The analgesics use is significantly less in the NOSES group than the conventional laparoscopy group, and the difference was significant (MD = 0.08; 95% CI: 0.03 to 0.26; $I^2=66\%$; $P=0.0005$). This meta-analysis seems to have the biggest relative strength of evidence due to statistical analysis of the results of the several case-studies and total number of patients.

Time of postoperative recovery of bowel function

In the case study by Jong *et al.* the average time to tolerate a soft diet was 3.6 days (range, 2–7 days) in patients that were undergoing transrectal NOSES in left hemicolectomy for tumors around the splenic flexure (CRC-NOSES VIB) (17). Gao *et al.* (18) described shorter time to postoperative flatus after robotic radical resection for high rectal cancer with transvaginal specimen extraction (40.9 ± 2.6 vs. 51.9 ± 2.9 hours, $t=12.049$, $P<0.001$).

Complications

Researchers described no significant difference in the incidence of postoperative complications between the CRC-NOSES and the conventional laparoscopy groups. Liu *et al.* explored the safety of NOSES with transanal specimen extraction (15). In this study data from 125 patients diagnosed with sigmoid colon and upper rectal cancer surgery was analyzed, and this article has great evidence strength to others due to total number of patient and precise selection by location of the tumor (sigmoid colon and upper rectum). The postoperative complication rate was 6.00% (3/50 patients) in the NOSES group. The complication rate was 8.00% (6/75 patients) in the conventional laparoscopy group. The difference in the incidence of postoperative complications between the two groups was not statistically significant ($P>0.05$). There was one case of anastomotic leakage in each group, and anastomotic healing occurred after fasting and circulatory washing. No secondary surgery was performed in this study. In meta-analysis by Xu *et al.* NOSES group had a lower incidence of total perioperative complications (10.3%) compared to conventional

laparoscopy group (19.4%) (odds ratio, OR 0.46; 95% CI: 0.32 to 0.66; $I^2 = 0\%$; $P<0.0001$) (16).

Oncological outcomes

The short-term advantages of NOSES are widely described. In recent studies, oncological outcomes were compared between NOSES-group and conventional laparoscopic surgery-group (19,20). Abovementioned studies also showed no statistically significant difference in the disease-free survival rate between the NOSES-group and the non-NOSES groups. In the case study by Kim *et al.* (21), no transvaginal access-site recurrence occurred after a median follow-up of 34.4 months. The 3-year disease-free survival was similar between two groups. Also, in the recent meta-analysis by Wang *et al.* (22) 3-year overall and disease-free survival in the NOSES group were comparable with those in the conventional laparoscopy group.

Zhou *et al.* (23) performed a prospective randomized controlled trial where postoperative survival rates were estimated. Patients with upper rectal or sigmoid colon cancer were randomized in a 1:1 ratio to the NOSES group and the conventional laparoscopy group. There were no statistically significant differences in the disease-free survival rate between the groups ($P>0.05$). Gao *et al.* (18) also followed-up patients with upper rectal cancer which underwent robotic radical resection and transvaginal NOSES. The mean followed-up period was 10 months in the no-incision group, and 14 months in the control group. No local recurrence and distant metastasis were found in both groups (18).

Results of a case study by Chang *et al.* (24) also showed that oncologic outcomes of laparoscopic anterior resection with NOSES for sigmoid and upper rectal cancer do not differ from conventional extraction. Of 392 eligible patients, 188 were matched (94 undergoing NOSES and 94 undergoing conventional extraction by minilaparotomy). Median follow-up was 50.3 months. The cumulative local recurrence risk at 5 years was 2.3% and 3.5% ($P=0.632$), whereas 5-year disease-free survival for all tumor stages was 87.3% and 82.0% ($P=0.383$) in the NOSES and conventional extraction groups.

Moreover, Xu *et al.* (16) performed meta-analysis including trials and analyzed studies comparing NOSES with conventional laparoscopy for sigmoid and rectal cancer. The analysis showed that NOSES was comparable to conventional laparoscopy in oncological safety. Three studies provided data on the 5-year disease-free survival (DFS) rate. There was no significant difference in 5-year

DFS between the NOSES and conventional laparoscopy groups [hazard ratio (HR) =0.86; 95% CI: 0.59 to 1.25; $I^2 = 0\%$; $P=0.43$]. Two studies provided data on the 5-year OS rate. There was no significant difference in 5-year OS between NOSES and conventional laparoscopy groups (HR =0.78; 95% CI: 0.43 to 1.40; $I^2=0\%$; $P=0.40$) (16).

Challenges

A few factors influence the feasibility of NOSES, but they are crucial for patient selection and standardized randomized trials, therefore, they cannot be ignored (25). Zhou *et al.* (23) conducted a retrospective study to define reasons that can lead to conversion of NOSES to transabdominal specimen extraction. Using the multivariate analyses authors received the following results: BMI, mesenteric thickness, maximal tumor diameter, and depth of tumor invasion were the factors influencing the feasibility of NOSES. These results correspond to indications and contraindications stated in the International consensus on NOSES for colorectal cancer (11) and are supported in the latest edition of NOSES Book published in 2021 (6).

Anastomotic leakage is a serious postoperative complication in colorectal cancer, and the risk factors for this complication after NOSE surgery have rarely been investigated. Due to the necessity to evaluate the predictive factors for anastomotic leakage after total laparoscopic resection with transrectal natural orifice specimen extraction for colorectal cancer, Zhou *et al.* (26) conducted the univariate analysis which showed that distance of anal verge (10.5 *vs.* 14.5 cm, $P=0.011$) duration of operation ≥ 140 min (71.4% *vs.* 29.4%, $P<0.001$) were associated with an increased incidence of anastomosis leakage. The multivariate analysis showed that a duration of operation ≥ 140 min (OR =5427, 95% CI: 1.355 to 21.727, $P=0.017$) was an independent risk factor for anastomosis leakage. Based on the results of the research of our multicenter study we may cautiously conclude that the problem is not specific to NOSES, even though the duration of these operations is longer than the conventional laparoscopic surgeries duration (27).

We have found only one case of laparoscopic colon cancer resection who developed vaginal recurrence after transvaginal specimen extraction (28) based on our search strategy. A 59-year-old female underwent laparoscopic left hemicolectomy due to left-sided colon adenocarcinoma, and the specimen was removed through the vagina. After

1 year, adenocarcinoma on the posterior vaginal wall was diagnosed, She had no recurrence or metastasis within the 3-year after the primary surgery. Incisional recurrence after NOSES may be considered among the complications. A case report for an individual patient cannot afford to evaluate probability of complication incidence, and it should be investigated further, but reports have incredible significance for researchers during implementing new surgical approach.

Above-mentioned Liu *et al.* study (15) also reported that the exfoliative cytology rate of the peritoneal wash fluid was 0 in the laparoscopic NOSES group compared to the conventional laparoscopy group. Also, the rates of the positive bacterial culture were measured, and it was not significant in both groups ($P>0.05$) (15).

Quality of the current evidence & pitfalls of studies in NOSES

Described studies have different place in the hierarchy of evidence. The design of the study, choosing measuring endpoints and number of included and excluded participants can affect the strength of the evidence, and we should evaluate them critically.

Leading surgical centers can become ambassadors in the new field of prospective investigations of differences in the results of open surgeries, laparoscopic interventions and NOSES. Certainly, this process requires standard research design and implementation of special protocols before recruitment of patients due to the necessity of getting accurate and reproducible results. One of these protocols has already been developed for comparison robotic NOSES versus traditional robotic-assisted surgery (29). The moment of randomization is also important, and our literature review showed that single randomized controlled trials of NOSES appear (30). At what point of surgery should be made a decision on traditional laparoscopy or NOSES during conducting a study?

Moreover, one of the challenges is the invention of the randomization method. It is also impossible to completely eliminate and accurately predict various intraoperative situations in which urgent necessity to change the chosen method emerges, for example, due to anatomical reasons, conversion to open surgery with laparotomy. Thus, sharing research protocols will make possible conduction reliable studies and obtain results reproducible in different clinical centers worldwide.

Conclusions

The advantages of NOSES including reduction in postoperative pain and wound complications, less use of postoperative analgesics, faster recovery of bowel function have been described in left-sided colon and upper rectal cancer treatment. Oncological outcomes do not differ with conventional laparoscopic surgery with specimen extraction via laparotomy.

We highlighted that NOSES success depends on the accessibility of high-quality surgical training, the importance of sharing experience with colleagues from centers worldwide and creating training programs for curious surgeons open to innovations. This will help to shorten the learning curve and improve the results of surgical treatment. The implementation of the surgeons' training programmes will facilitate the spread of the revolutionary NOSES approach to ensure the best results for our patients. NOSES is all about complexity, passion and the art of modern surgery.

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