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Systematic Review

Natural orifice *versus* transabdominal specimen extraction in laparoscopic surgery for colorectal cancer: meta-analysis

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Abstract

Background: Natural orifice specimen extraction (NOSE) is a technique that involves collecting a specimen for extraction through a natural opening avoiding a mini-laparotomy incision. The aim of this study was to compare NOSE and transabdominal specimen extraction in laparoscopic (LAP) colorectal cancer surgery for postoperative outcomes and oncological safety.

Method: A systematic search was conducted in five electronic databases from inception till October 2020. Articles were selected based on the inclusion criteria (studies comparing LAP and NOSE colorectal surgeries reporting at least one of the outcomes) and analysed. Primary outcomes included postoperative complications, pathological results (resection margins and lymph node collection), and oncological outcomes. Secondary outcomes included operating time, blood losses, use of analgesics, functional recovery, duration of hospital stay, and cosmetic results. Fixed and random-effect models were used to measure the pooled estimates.

Results: Nineteen studies involving a total of 3432 participants were analysed (3 randomized clinical trials (RCTs) and 16 retrospective non-randomized studies). Pooled results showed significantly reduced postoperative complications (OR 0.54; 95 per cent c.i. 0.44 to 0.67; $P < 0.00001$). Pathological outcomes of NOSE were comparable to LAP with no significant difference noted in terms of resection margins ($P > 0.05$) and lymph node collection (weighted mean difference (WMD) −0.47; 95 per cent c.i. −0.94 to 0; $P = 0.05$). Pooled analysis demonstrated comparable long-term outcomes in terms of cancer recurrence (OR 0.94; 95 per cent c.i. 0.63 to 1.39; $P = 0.75$), 5-year disease-free survival (HR 0.97; 95 per cent c.i. 0.73 to 1.29; $P = 0.83$), and overall survival (HR 0.93, 95 per cent c.i. 0.58 to −1.51; $P = 0.78$). Finally, the NOSE group had decreased use of additional analgesia after surgery and earlier resumption of oral intake when compared with LAP (respectively OR 0.28; 95 per cent c.i. 0.20 to 0.37; $P < 0.00001$ and WMD −0.35; 95 per cent c.i. −0.54 to −0.15; $P = 0.0005$).

Conclusion: This meta-analysis showed that in comparison with LAP, NOSE decreases severe postoperative morbidity while improving postoperative recovery without compromising oncological safety, but it is limited by the small number of RCTs performed in this field.

Introduction

The introduction of laparoscopy in early 20th century has revolutionized surgery. Following the increased use of laparoscopy in colorectal surgery, the focus has now shifted to further refinement of this technique[1]. Despite its established advantages, morbidity associated with mini-laparotomy incision for the specimen extraction (wound infections, dehiscence, and incisional hernias) in conventional laparoscopy has been reported[2]. To mitigate these complications, natural orifice specimen extraction (NOSE) has been developed, whereby a natural hollow viscus with already established communication to the outside such as the anus or vagina, is used for bowel extraction. This obviates the need for the mini-laparotomy incision and its associated complications; also, it reduces the surgical trauma at the specimen extraction site with a possible decrease in postoperative pain, earlier gastrointestinal function, and decrease duration of hospital stay[3]. While the theoretical advantage of NOSE over transabdominal specimen extraction in conventional laparoscopy (LAP) in benign colorectal disease has been proven, there is a lack of conclusive evidence on its benefits in colorectal cancer (CRC). There have been bacteriological concerns in view of breaches in peritoneal sterility during enterotomy as well as concerns on implantation of tumour at the specimen extraction site[4]. To date, most studies[5–9] have included a mix of both benign and malignant colorectal disease or failed to compare oncological outcomes, which are important particularly in the context of colorectal malignancy. To address this, a systematic review and meta-analysis was conducted with the aim to evaluate the safety (in terms of postoperative complications), pathological (with respect to lymph node harvest and resection margins), and oncological outcomes (in terms of cancer recurrence and survival) of NOSE compared with LAP for CRC.

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Methods

Study design

The protocol was compiled and registered in PROSPERO (CRD42020222699)[10]. The review was reported in accordance with PRISMA-P standards[11]. Methodological quality was ensured by following AMSTAR (assessing the methodological quality of systematic review) guidelines[12].

A systematic search for published articles was conducted in November 2020 in five electronic databases (Cochrane Library, Cumulative Index to Nursing and Allied Health Literature, Embase, MEDLINE, and SCOPUS) from their inception till the end of October 2020. The keywords and Medical Subject Headings terms used for the search strategy were specimen extraction AND laparoscop* AND (colo* OR rect*). References of accepted articles were also manually screened for potentially relevant studies to ensure that no additional publications were missed.

The selection criteria followed the PICOS (participants, intervention, comparison, outcomes, and study design) framework[13].

- **Participants:** patients over 18 years of age diagnosed with CRC
- **Intervention:** laparoscopic surgery with NOSE (transanal or transvaginal)
- **Comparator:** conventional laparoscopic surgery with transabdominal specimen extraction
- **Primary outcomes:**
  - Postoperative complications categorized according to Clavien–Dindo classification (overall complications, wound infections, intraperitoneal abscess, and intra-abdominal abscess, pneumonia, urinary complications, anastomotic leak, ileus, intestinal obstruction, venous thromboembolism, haemorrhage, fistula formation, incisional hernia, and reoperation)
  - Pathological results (lymph node collection and resection margins)
  - Oncological outcomes: local recurrence, disease-free survival, and overall survival
- **Secondary outcomes:** intraoperative blood loss, operating time, postoperative pain, additional analgesia used after surgery, gastrointestinal function recovery, resumption of oral intake, duration of hospital stay, and cosmetic results.
- **Study design:** full-text publications of comparative quantitative studies reporting at least one of the outcomes.

The search was not time-limited but it was restricted to articles in the English language. Studies were excluded if the surgical procedure was not as specified in the inclusion criteria (such as open, robotic, single-port surgery, or transanal total mesorectal excision) or if the publication type was deemed unsuitable (example descriptive/technical review or conference abstracts). Studies performed on cadaveric or animal models were also excluded.

Study selection and data extraction

Articles were selected after a thorough screening process that sequentially assessed the title, abstract, and subsequently the full-text article according to the inclusion and exclusion criteria. Duplicate studies were removed. Data extraction was performed by two members of the research team and authors were contacted when missing data were noted. Discrepancies were discussed until consensus was reached. A PRISMA flow chart[11] summarizing the study selection was compiled. A data extraction form (*Table S1*) was prepared based on the review aims.

Quality assessment

The quality of the articles was assessed using validated risk of bias assessment tools. The Cochrane risk of bias-2 (RoB-2) tool[14] was used for randomized trials, whereas retrospective non-randomized trials were assessed using risk of bias in non-randomized studies of interventions (ROBINS-I) tool[15].

Data analysis

Difference in effect sizes was assessed using weighted mean difference (WMD) for continuous variables by the application of the inverse variance method. For dichotomous variables, the Mantel–Haenszel method was used to calculate the OR. Studies that did not provide the mean and s.d. were calculated as described previously[16]. For survival analysis, when studies did not provide the HR, this was calculated using the method of Tierney[17] using data extraction from survival curves. Heterogeneity was assessed using Cochrane Q test, I^2, and τ^2 and this determined whether a random-effect or fixed-effect model was applied. Considering potential heterogeneity among studies, the results were pooled using a random-effects model. If $P > 0.1$ and $I^2 < 50$ per cent, heterogeneity was not considered as significant and a fixed-effects model was used[18]. Studies were subdivided into prespecified clinically relevant parameters to perform subgroup analysis with a $P < 0.1$ used to determine statistical significance[19]. Meta-regression of significant outcomes was also conducted. Sensitivity analysis was then used to assess the reliability of the results. Publication bias was assessed using funnel plots. Statistical significance was set at $P < 0.05$. Data were analysed using Review Manager 5 and the statistical programming language R.

Results

The literature search yielded 326 articles, as shown in the PRISMA flow diagram (*Fig. 1*). A total of 19 studies[20–38] met the inclusion criteria and were included in this systematic review. The characteristics of the included studies are shown in *Table 1*. Sixteen of the included studies are retrospective non-randomized studies and the other three are prospective randomized clinical trials (RCT). A total of 3432 participants were included in this meta-analysis: 1644 participants in the NOSE group and 1788 participants in LAP. Fourteen studies assessed transanal NOSE, three studies evaluated transvaginal NOSE, and another two studies included both transanal and transvaginal NOSE approaches. Basic patient and tumour characteristics are shown in *Tables S2 and S3* respectively. Most participants included in this analysis had left-sided tumours ($n = 3243$) and mainly rectal tumours ($n = 2620$).

Quality of included studies

Following assessment using the RoB-2 tool for RCTs, two RCTs were deemed to have low risk of bias and one RCT was considered to have moderate risk of bias. The ROBINS-I tool identified the most studies ($n = 10$) with an overall low risk of bias with only one study having an overall serious risk of bias, *Fig. 2*.

Primary outcomes

All included studies reported the incidence of postoperative complications, *Fig. 3*. Pooled analysis showed that the NOSE

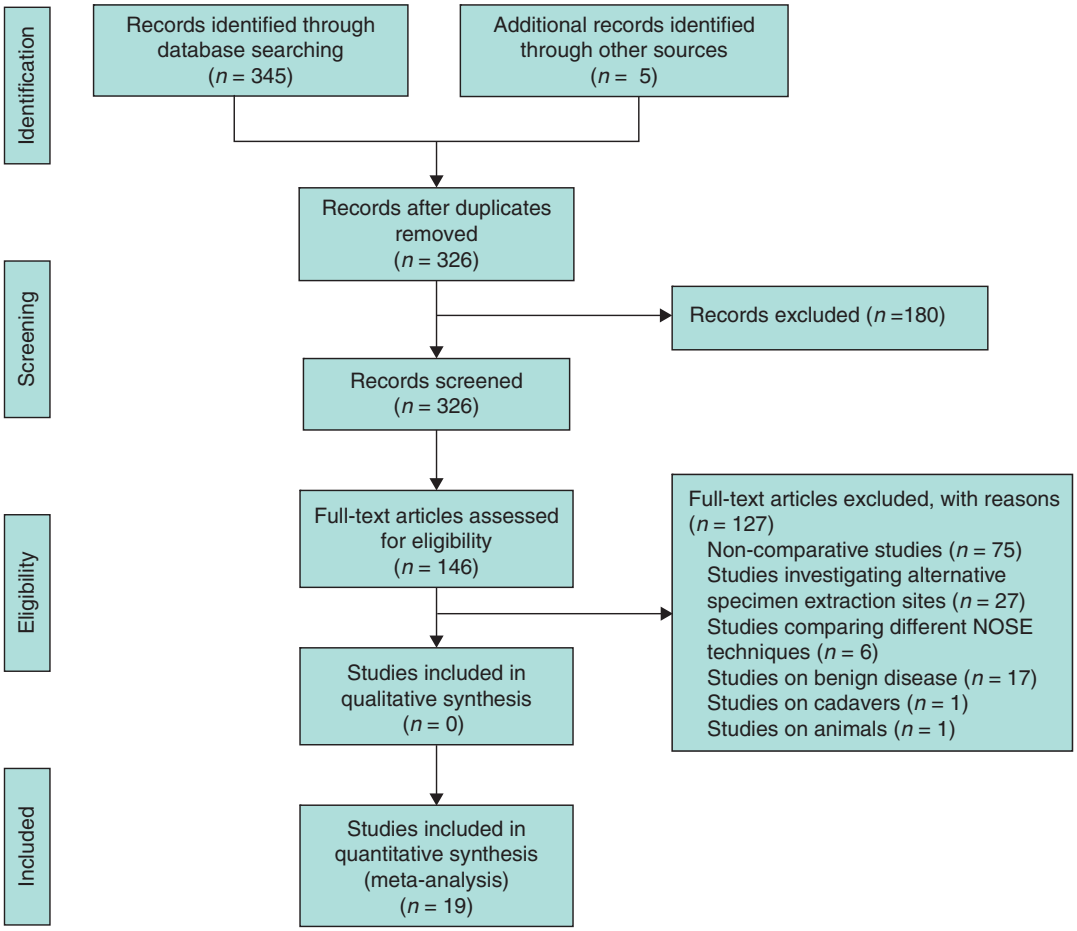


Fig. 1 Outline of the literature review and selection process. NOSE, natural orifice specimen extraction.[11]

group had a statistically significant lower rate of complications compared with the LAP group (OR 0.54; 95 per cent c.i. 0.44 to 0.67; $P < 0.00001$). A low level of heterogeneity was detected ($I^2 =$ 4 per cent) and a fixed-effects model was used. There was no significant difference in Clavien–Dindo classification grade I– II between the NOSE and LAP groups (OR 1.25; 95 per cent c.i. 0.28 to 5.64; $P = 0.77$); however, on comparing Clavien–Dindo grade III–IV complications, based on five studies, a significant difference between the NOSE and LAP group was noted, with the NOSE group demonstrating fewer complications (OR 0.60; 95 per cent c.i. 0.38 to 0.95; $P = 0.03$) compared with LAP.

Analysis of individual postoperative complications was performed. In all outcomes, the fixed-effects model was used as heterogeneity was not considered as significant. Sixteen studies reported data on wound infection. Pooled analysis, based on 2957 patients, showed a significant difference between the NOSE and LAP group, with the NOSE group demonstrating a lower rate of wound infection ($n = 2957$; OR 0.17; 95 per cent c.i. 0.10 to 0.29; $P < 0.00001$; $I^2 = 0$ per cent), *Fig. 3*. The pooled analysis showed no statistically significant difference between the NOSE and LAP group in terms of other infectious postoperative complications such as intraperitoneal infection ($n = 649$; OR 0.75; 95 per cent c.i. 0.28 to 2.05; $P = 0.57$) and intra-abdominal abscess formation ($n = 908$; OR 0.77; 95 per cent c.i. 0.29 to 2.10; $P = 0.62$), lung ($n = 1799$; OR 1.06; 95 per cent c.i. 0.56 to 2.01; $P =$ 0.85), and urinary tract infection rate ($n = 860$; OR 2.05; 95 per cent c.i. 0.72 to 5.85; $P = 0.18$). Data from 13 studies, covering 2636 patients showed no significant difference in anastomotic leak rates between the NOSE and LAP group ($n = 2636$; OR 1.03; 95 per cent c.i. 0.69 to 1.52; $P = 0.90$). Similarly the pooled analysis demonstrated no significant difference in terms of urinary retention ($n = 635$; OR 0.73; 95 per cent c.i. 0.29 to 1.85; $P = 0.51$), postoperative ileus ($n = 1959$; OR 0.58; 95 per cent c.i. 0.26 to 1.30; $P = 0.19$), intestinal obstruction ($n = 566$; OR 2.37; 95 per cent c.i. 0.93 to 6.05 $P = 0.07$), venous thromboembolism ($n =$ 492; OR 1.82; 95 per cent c.i. 0.38 to 8.63; $P = 0.45$), postoperative haemorrhage (n = 2146; OR 1.06; 95 per cent c.i. 0.58 to 1.94; $P = 0.84$), fistula formation rate ($n = 406$; OR 1.00; 95 per cent c.i. 0.14 to 7.20; $P = 1.00$), and incisional hernia rates ($n = 860$; OR 0.67; 95 per cent c.i. 0.17 to 2.64; $P = 0.56$) between the NOSE and LAP group. Reoperation rates were comparable between the NOSE and LAP groups with no significant difference noted ($n = 1216$; OR 0.92; 95 per cent c.i. 0.32 to 2.66; $P = 0.88$).

Pathological outcomes

Fourteen studies reported the number of collected lymph nodes. There was no significant difference in lymph node collection between the NOSE and LAP group (WMD −0.47; 95 95 per cent c.i. −0.94 to 0.00; $P = 0.05$; $I^2 = 0$ per cent), *Fig. 4*. The mean number of dissected lymph nodes was 17.8 in NOSE and 17.2 in LAP group. Additionally, there was no significant difference between NOSE and LAP group in terms of proximal (m 0.55;

Table 1 Characteristics of included studies

Author	Publication year	Country	Study design	Total patients	Sample size LAP	Sample size NOSE	Specimen extraction site
Bu *et al.* [20]	2020	China	RCT	92	46	46	TA
Chang *et al.* [21]	2020	Korea	RNR	188	94	94	TA
Ouyang *et al.* [22]	2020	China	RNR	185	89	96	TA
Zhou *et al.* [23]	2020	China	RNR	344	172	172	TA
Zhou *et al.* [24]	2020	China	RCT	219	119	100	TA
Zhu *et al.* [25]	2020	China	RCT	223	119	104	TA
Ding *et al.* [26]	2019	China	RNR	86	43	43	TA
Hu *et al.* [27]	2019	China	RNR	52	26	26	TA
Li *et al.* [28]	2019	China	RNR	62	31	31	TV
Liu *et al.* [29]	2019	China, Russia	RNR	768	412	356	TA, TV
Wang *et al.* [30]	2019	China	RNR	67	37	30	TA
Zhou *et al.* [31]	2019	China	RNR	104	52	52	TA
Ng *et al.* [32]	2018	China	RNR	73	38	35	TA
Park *et al.* [33]	2018	Korea	RNR	276	138	138	TA, TV
Denost *et al.* [34]	2015	France	RNR	220	122	98	TA
Hisada *et al.* [35]	2014	Japan	RNR	70	50	20	TA
Kim *et al.* [36]	2014	Korea	RNR	116	58	58	TV
Xingmao *et al.* [37]	2014	China	RNR	197	132	65	TA
Park *et al.* [38]	2011	Korea	RNR	68	34	34	TV

RNR, retrospective non-randomized study; RCT, randomized clinical trial; LAP, conventional laparoscopy with transabdominal specimen extraction; NOSE, natural orifice specimen extraction; TA, transanal; TV, transvaginal.

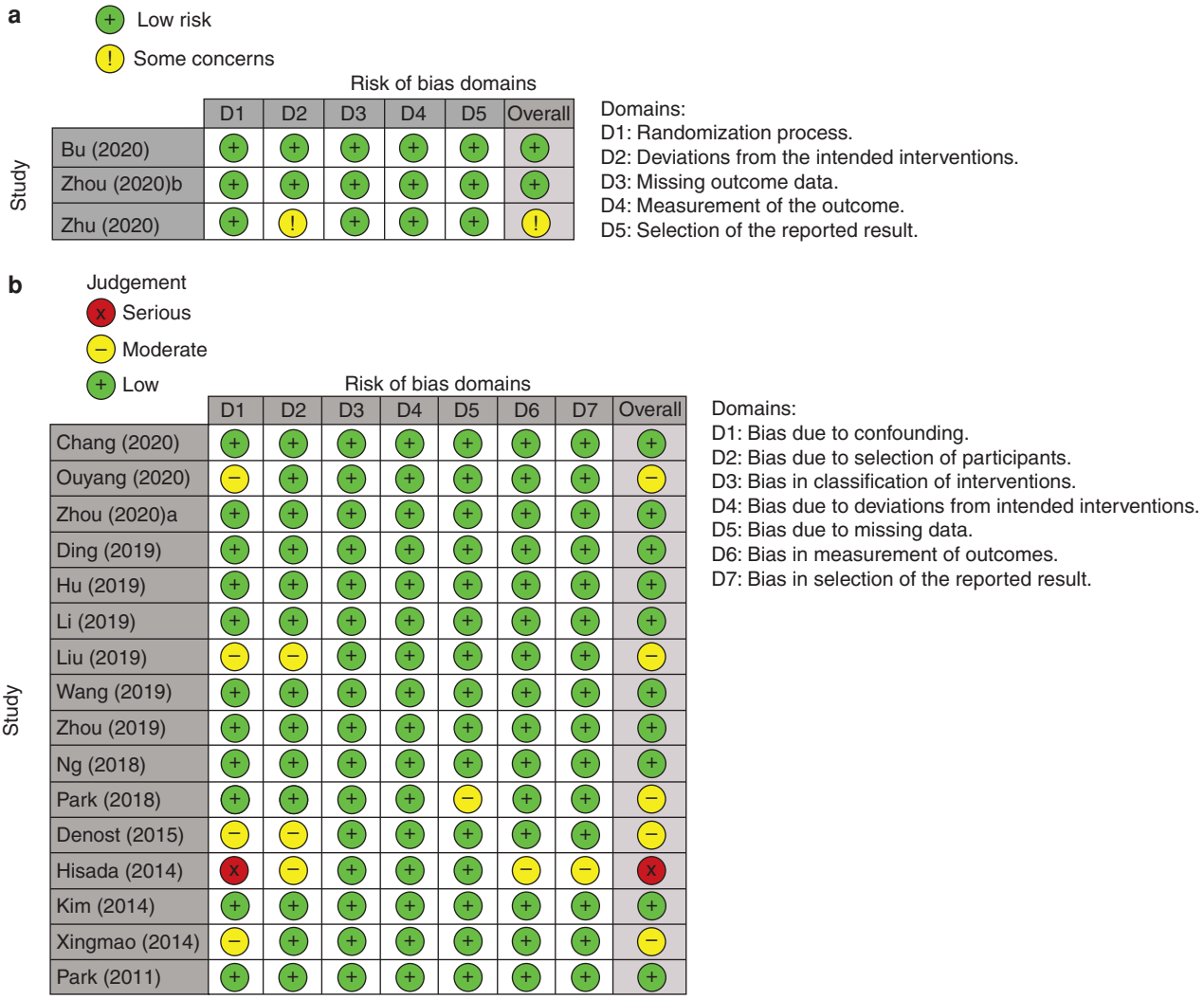


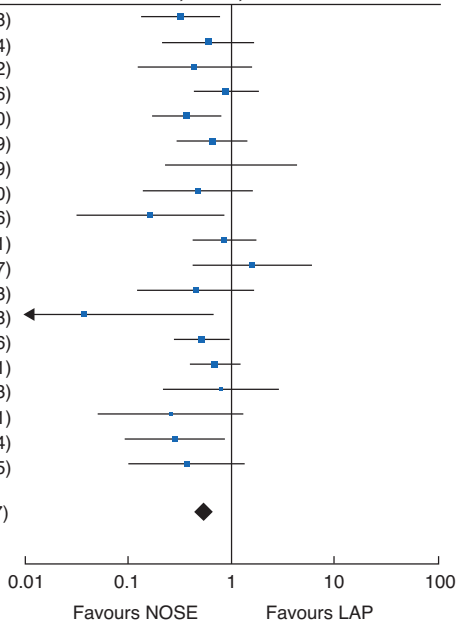
Fig. 2 Risk of bias
a Randomized clinical trials assessed using RoB-2 tool. **b** Non-randomized studies using the ROBINS-I tool.

a

Study or subgroup	NOSE Events	NOSE Total	LAP Events	LAP Total	Weight (%)	OR M-H, Fixed, 95% c.i.
Bu *et al.*[20]	22	46	34	46	7.2	0.32 (0.13, 0.78)
Chang *et al.*[21]	7	94	11	94	4.1	0.61 (0.22, 1.64)
Ouyang *et al.*[22]	4	96	8	89	3.2	0.44 (0.13, 1.52)
Zhou *et al.*[23]	17	172	19	172	6.9	0.88 (0.44, 1.76)
Zhou *et al.*[24]	11	122	25	119	9.3	0.37 (0.17, 0.80)
Zhu *et al.*[25]	12	104	20	119	6.7	0.65 (0.30, 1.39)
Ding *et al.*[26]	4	43	4	43	1.5	1.00 (0.23, 4.29)
Hu *et al.*[27]	6	26	10	26	3.1	0.48 (0.14, 1.60)
Li *et al.*[28]	2	31	9	31	3.4	0.17 (0.03, 0.86)
Liu *et al.*[29]	15	356	20	412	7.2	0.86 (0.43, 1.71)
Wang *et al.*[30]	6	30	5	37	1.5	1.60 (0.44, 5.87)
Zhou *et al.*[31]	4	52	8	52	3.0	0.46 (0.13, 1.63)
Ng *et al.*[32]	0	35	10	38	4.0	0.04 (0.00, 0.68)
Park *et al.*[33]	21	138	35	138	12.0	0.53 (0.29, 0.96)
Denost *et al.*[34]	42	122	42	98	12.4	0.70 (0.40, 1.21)
Hisada *et al.*[35]	4	20	12	50	2.2	0.79 (0.22, 2.83)
Kim *et al.*[36]	2	58	7	58	2.7	0.26 (0.05, 1.31)
Xingmao *et al.*[37]	4	65	25	132	6.3	0.28 (0.09, 0.84)
Park *et al.*[38]	4	34	9	34	3.2	0.37 (0.10, 1.35)
Total (95% c.i.)		1644		1788	100.0	0.54 (0.44, 0.67)
Total events	187		313			

Heterogeneity: $\chi^2 = 18.67$, 18 d.f., $P = 0.41$; $I^2 = 4\%$

Test for overall effect: $Z = 5.76$, $P < 0.00001$



b

Study or subgroup	NOSE Events	NOSE Total	LAP Events	LAP Total	Weight (%)	OR M-H, Random, 95% c.i.
Chang *et al.*[21]	3	94	6	94	30.9	0.48 (0.12, 1.99)
Ng *et al.*[32]	35	35	28	38	16.6	26.16 (1.47, 465.77)
Park *et al.*[33]	11	138	20	138	38.1	0.51 (0.23, 1.11)
Park *et al.*[38]	34	34	33	34	14.3	3.09 (0.12, 78.55)
Total (95% c.i.)		301		304	100.0	1.25 (0.28, 5.64)
Total events	83		87			

Heterogeneity: $\tau^2 = 1.39$; $\chi^2 = 8.87$, 3 d.f., $P = 0.03$; $I^2 = 66\%$

Test for overall effect: $Z = 0.29$, $P = 0.77$

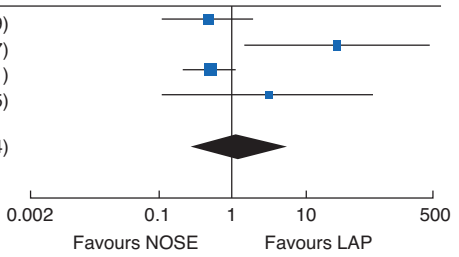


Fig. 3 Forest plots of postoperative complications
a Overall complications. **b** Postoperative complications based on Clavien–Dindo classification I– II. **c** Postoperative complications based on Clavien–Dindo classification III–IV. **d** Postoperative wound infection. LAP, laparoscopy; NOSE, natural orifice specimen extraction.

95 per cent c.i. −0.06 to 1.16; $P = 0.08$) and distal resection margins (WMD −0.13; 95 per cent c.i. −0.42 to 0.16; $P = 0.39$) as obtained from data in 6 and 7 studies respectively, *Fig. 4*.

Oncological outcomes

Twelve studies reported data on total recurrence rates, including local and distant recurrence. Pooled analysis on 1500 patients showed no significant difference between NOSE and LAP group in terms of total (local and distant) recurrence (OR 0.94; 95 per cent c.i. 0.63 to 1.39; $P = 0.75$; $I^2 = 0$ per cent). Similarly, analysis of six studies which reported outcomes on local recurrence at 3 years (OR 0.84; 95 per cent c.i. 0.40 to 1.73; $P = 0.63$) and 5 years (OR 0.94; 95 per cent c.i. 0.48 to 1.84; $P = 0.85$) showed no statistically significant difference amongst both groups, *Fig. 5*.

Data on disease-free survival for three and five years was obtained from 7 and 6 studies respectively. Pooled analysis showed no significant difference between NOSE and LAP group in terms of disease-free survival at 3 years (HR 0.85; 95 per cent c.i. 0.66 to 1.09 $P = 0.19$) and 5-years (HR 0.97; 95 per cent c.i. 0.73 to 1.29; $P = 0.83$). No heterogeneity was detected amongst the included studies ($I^2 = 0$ per cent), *Fig. 5*.

Three and five-year overall survival data was obtained from five studies. No significant difference was observed between NOSE and LAP group in 3-year (HR 0.99; 95 per cent c.i. 0.59 to 1.66; $P = 0.96$) and 5-year overall survival (HR 0.93; 95 per cent c.i. 0.58 to 1.51; $P = 0.78$). Included studies were homogenous with an I^2 of 0 per cent, *Fig. 5*.

Secondary outcomes group

A total of 16 studies reported data on intraoperative blood loss. This included a total of 2911 patients, with 1368 in NOSE group and 1543 in LAP group. The pooled data showed a statistically significant decreased blood loss in NOSE compared with the LAP group (WMD −13.98; 95 per cent c.i. −21.83 to −6.14; $P = 0.0005$); however, it should be noted that substantial heterogeneity is present among the included studies with I^2 of 84 per cent.

Apart from two studies[22,34] all other studies included data on operating time. Pooled analysis showed that the NOSE group had a statistically significant prolonged operating time, with the overall operating time being 10 min less in the LAP group (WMD 10.52; 95 per cent c.i. 4.72 to 16.31; $P = 0.0004$). However, the effect of heterogeneity cannot be ignored as substantial

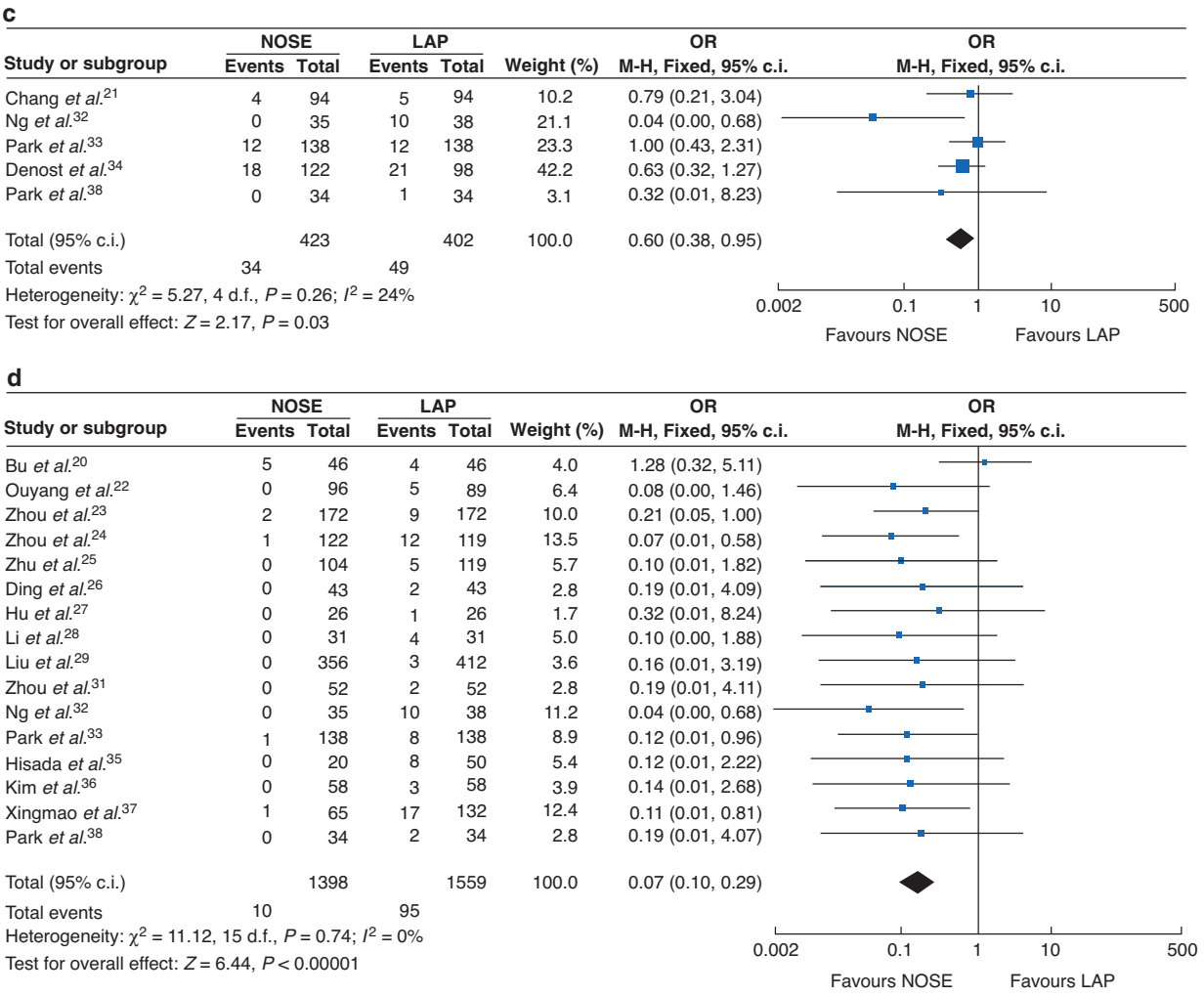


Fig. 3 Continued

heterogeneity was noted among included studies with I^2 of 76 per cent.

Postoperative pain was assessed using a visual analogue scale. Twelve studies reported pain scores within the first 24 h after surgery, eight studies reported pain scores on postoperative day (POD) 3, and four studies reported data on POD 5. Pooled analysis showed that during the postoperative interval, patients who had NOSE experienced less pain, scoring statistically significant lower pain scores compared with the LAP group on POD 1 (WMD −1.86; 95 per cent c.i. −2.34 to −1.38; $P < 0.00001$), POD 3 (WMD −1.57; 95 per cent c.i. −2.08 to −1.05; $P < 0.00001$), and POD 5 (WMD −1.11; 95 per cent c.i. −2.06 to −0.17; $P = 0.02$). Considerable heterogeneity was detected with an ($I^2 \geq 95$ per cent). Nine studies reported outcomes on additional analgesia used after surgery. The NOSE group had a decreased use of additional analgesia after surgery when compared with LAP (OR 0.28; 95 per cent c.i. 0.20 to 0.37), which was statistically significant with $P < 0.00001$. A low level of heterogeneity was detected with an I^2 of 23 per cent (*Fig. 6*).

In this meta-analysis, studies provided data on the passage of the first flatus (nine studies) or defaecation (three studies) as part of bowel function recovery assessment. When both outcomes were recorded in the same study, the time to first flatus was chosen in preference. The NOSE group had a statistically significant improvement in gastrointestinal function recovery (WMD −0.53; 95 per cent c.i. −0.78 to −0.28; $P < 0.0001$), as demonstrated by a statistically significant shorter time for the first passage of flatus (WMD −0.43; 95 per cent c.i. −0.68 to −0.19; $P = 0.0006$) and first defaecation (WMD −0.66; 95 per cent c.i. −1.08 to −0.24; $P = 0.002$) compared with the LAP group. Substantial heterogeneity was noted among the included studies with $I^2 > 80$ per cent. Only five studies reported a resumption of a regular diet in days, as part of the study outcome. The pooled analysis showed that patients in the NOSE group had statistically significant earlier resumption of oral intake (WMD −0.35; 95 per cent c.i. −0.54 to −0.15; $P = 0.0005$, $I^2 = 33$ per cent) compared with the LAP group (*Fig. 6*).

All studies except one[34] reported patients' duration of hospital stay postoperatively. Findings from the pooled analysis revealed a significant shorter duration of hospital stay in the NOSE compared with the LAP group (WMD −1.21; 95 per cent c.i. −1.60 to −0.81; $P < 0.00001$). Substantial heterogeneity among the studies was detected with an I^2 of 79 per cent.

Three studies reported data on cosmesis based on a score ranging from 1 (poor) to 10 (excellent). Pooled analysis showed a significant difference between the NOSE and LAP group with the mean cosmesis score estimated to be 1.52 points higher (95 per cent c.i. 1.17 to 1.87) for patients undergoing NOSE compared

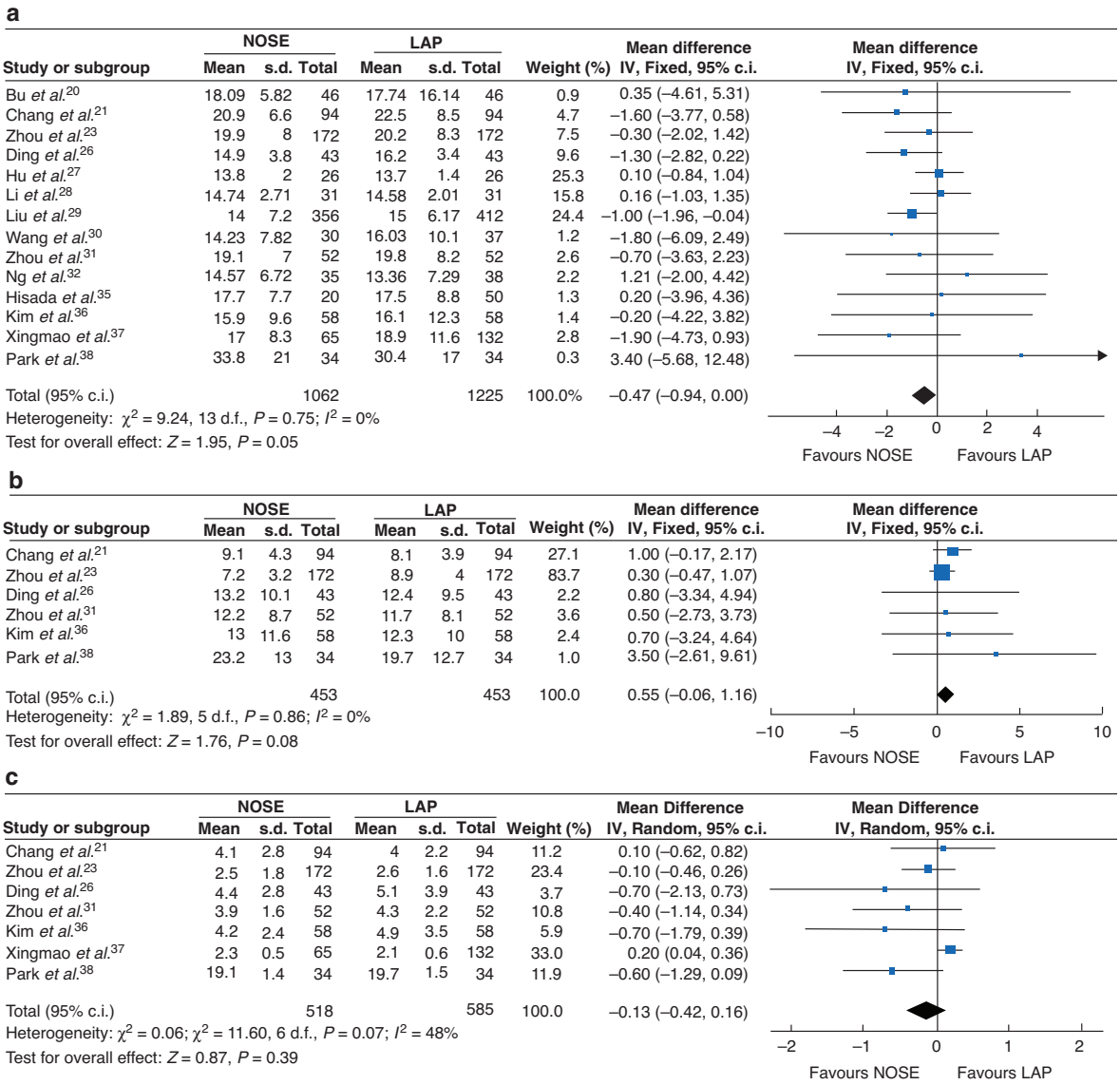


Fig. 4 Forest plot of pathological outcomes
a Lymph node collection. **b** Proximal resection margin. **c** Distal resection margin. LAP, laparoscopy; NOSE, natural orifice specimen extraction.

with patients undergoing LAP ($P < 0.00001$). Another three studies assessed patients' satisfaction with the appearance of the abdominal wall. Similar to the cosmetic outcome findings, patients in the NOSE group were more satisfied with their abdominal wall appearance after surgery (OR 40.02; 95 per cent c.i. 1.70 to 941.27; $P = 0.02$). Substantial heterogeneity with an I^2 of 81 per cent was noted among the included studies.

Subgroup analysis

In this meta-analysis, subgroup analysis was performed based on specimen extraction site (transanal and transvaginal specimen extraction) (*Table S4*). This showed that there is a statistically significant subgroup effect for intraoperative blood loss ($P = 0.01$, $I^2 = 83.9$ per cent) and distal resection margin ($P = 0.04$, $I^2 = 76.7$ per cent) when classified according to specimen site extraction in favour of NOSE (*Fig. S1*).

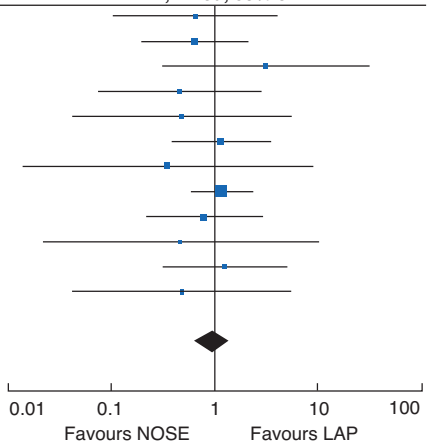
Meta-regression analysis

Meta-regression of patient characteristics (age, BMI, and ASA grade I–III) was conducted, with outcomes that were significant in the primary analysis (*Table S5*). Most of the meta-regressions conducted showed no statistically significant relationship between effect size and patient characteristics. A negative association between BMI and wound infection ($\beta = -1.1094$, s.e. 0.3193, $P = 0.0046$), BMI and additional analgesia ($\beta = -0.4132$, s.e. 0.1508, $P = 0.0289$), ASA grade I and resumption of oral intake ($\beta = -0.0152$, s.e. 0.0072, $P = 0.0363$) and between ASA grade III and pain on POD 1 ($\beta = -0.0250$, s.e. 0.0086, $P = 0.0036$). However, a significant positive relationship was observed between ASA grade I and operating time ($\beta = 0.1693$, s.e. 0.0614, $P = 0.0058$). ASA grade I–II and gastrointestinal function recovery (ASA grade I, $\beta = 0.0053$, s.e. 0.0009, $P < 0.0001$; ASA grade II $\beta = 0.0030$, s.e. 0.0015, $P = 0.0479$) and ASA grade I and time for first passage of flatus ($\beta = 0.0050$, s.e. 0.0008, $P < 0.0001$).

a

Study or subgroup	NOSE Events	NOSE Total	LAP Events	LAP Total	Weight (%)	OR M-H, Fixed, 95% c.i.
Chang *et al.*[21]	2	94	3	94	5.6	0.66 (0.11, 4.04)
Ouyang *et al.*[22]	5	96	7	89	13.2	0.64 (0.20, 2.11)
Ding *et al.*[26]	3	43	1	43	1.8	3.15 (0.31, 31.55)
Hu *et al.*[27]	2	26	4	26	7.1	0.46 (0.08, 2.75)
Li *et al.*[28]	1	31	2	31	3.7	0.48 (0.04, 5.62)
Zhou *et al.*[31]	8	52	7	52	11.4	1.17 (0.39, 3.50)
Ng *et al.*[32]	0	35	1	38	2.7	0.35 (0.01, 8.93)
Park *et al.*[33]	22	138	19	138	30.7	1.19 (0.61, 2.31)
Denost *et al.*[34]	5	122	5	98	10.2	0.79 (0.22, 2.83)
Hisada *et al.*[35]	0	20	2	50	2.7	0.47 (0.02, 10.29)
Kim *et al.*[36]	5	58	4	58	7.0	1.27 (0.32, 5.00)
Park *et al.*[38]	1	34	2	34	3.7	0.48 (0.04, 5.61)
Total (95% c.i.)		749		751	100.0	0.94 (0.63, 1.39)
Total events	54		57			

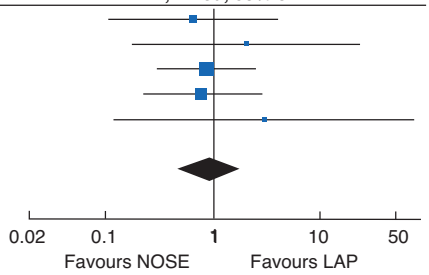
Heterogeneity: $\chi^2 = 4.21$, 11 d.f., $P = 0.96$; $I^2 = 0\%$
Test for overall effect: $Z = 0.32$, $P = 0.75$



b

Study or subgroup	NOSE Events	NOSE Total	LAP Events	LAP Total	Weight (%)	OR M-H, Fixed, 95% c.i.
Chang *et al.*[21]	2	94	3	94	17.0	0.66 (0.11, 4.04)
Zhou *et al.*[31]	2	52	1	52	5.6	2.04 (0.18, 23.22)
Park *et al.*[33]	7	138	8	138	43.9	0.87 (0.31, 2.46)
Denost *et al.*[34]	5	122	5	98	30.7	0.79 (0.22, 2.83)
Kim *et al.*[36]	1	58	0	58	2.8	3.05 (0.12, 76.48)
Total (95% c.i.)		464		440	100.0	0.94 (0.48, 1.84)
Total events						

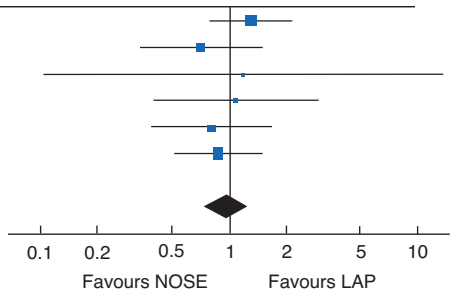
Heterogeneity: $\chi^2 = 1.14$, 4 d.f., $P = 0.89$; $I^2 = 0\%$
Test for overall effect: $Z = 0.19$, $P = 0.85$



c

Study or subgroup	log (HR)	s.e.	Weight (%)	HR IV, Fixed, 95% c.i.
Bu *et al.*[20]	0.27	0.26	31.3	1.31 (0.79, 2.18)
Chang *et al.*[21]	–0.35	0.38	14.7	0.70 (0.33, 1.48)
Li *et al.*[28]	0.17	1.24	1.4	1.19 (0.10, 13.47)
Zhou *et al.*[31]	0.08	0.51	8.1	1.08 (0.40, 2.94)
Park *et al.*[33]	–0.21	0.37	15.5	0.81 (0.39, 1.67)
Denost *et al.*[34]	–0.14	0.27	29.0	0.87 (0.51, 1.48)
Total (95% c.i.)			100.0	0.97 (0.73, 1.29)

Heterogeneity: $\chi^2 = 2.52$, 5 d.f., $P = 0.77$; $I^2 = 0\%$
Test for overall effect: $Z = 0.21$, $P = 0.83$



d

Study or subgroup	log (HR)	s.e.	Weight (%)	HR IV, Fixed, 95% c.i.
Bu *et al.*[20]	0.09	0.68	13.1%	1.09 (0.29, 4.15)
Chang *et al.*[21]	–0.05	0.41	36.0%	0.95 (0.43, 2.12)
Li *et al.*[28]	1.01	1.2	4.2%	2.75 (0.26, 28.85)
Zhou *et al.*[31]	0.29	0.75	10.8%	1.34 (0.31, 5.81)
Denost *et al.*[34]	–0.38	0.41	36.0%	0.68 (0.31, 1.53)
Total (95% c.i.)			100.0%	0.93 (0.58, 1.51)

Heterogeneity: $\chi^2 = 1.67$, 4 d.f., $P = 0.80$; $I^2 = 0\%$
Test for overall effect: $Z = 0.28$, $P = 0.78$

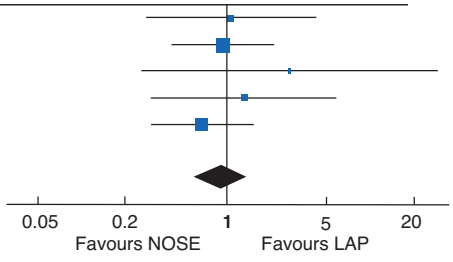


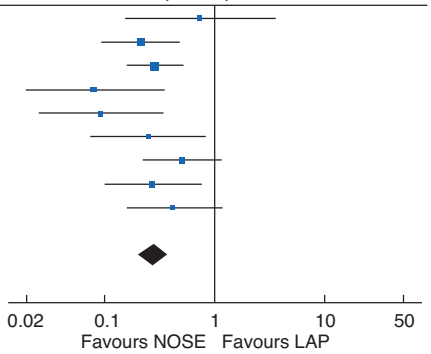
Fig. 5 Forest plots of oncological outcomes at 5 years
a Total recurrence. **b** Local recurrence. **c** Disease-free survival. **d** Overall survival. LAP, laparoscopy; NOSE, natural orifice specimen extraction.

a

Study or subgroup	NOSE Events	NOSE Total	LAP Events	LAP Total	Weight (%)	OR M-H, Fixed, 95% c.i.
Bu *et al.*[20]	42	46	43	46	2.2	0.73 (0.15, 3.47)
Ouyang *et al.*[22]	9	96	29	89	16.3	0.21 (0.09, 0.48)
Zhou *et al.*[23]	19	172	52	172	27.6	0.29 (0.16, 0.51)
Hu *et al.*[27]	3	26	16	26	8.5	0.08 (0.02, 0.34)
Li *et al.*[28]	4	31	19	31	9.9	0.09 (0.03, 0.33)
Zhou *et al.*[31]	4	52	13	52	7.2	0.25 (0.08, 0.83)
Kim *et al.*[36]	13	58	21	58	9.7	0.51 (0.22, 1.15)
Xingmao *et al.*[37]	5	65	31	132	11.3	0.27 (0.10, 0.74)
Park *et al.*[38]	16	34	23	34	7.3	0.43 (0.16, 1.14)
Total (95% c.i.)		580		640	100.0	0.28 (0.20, 0.37)
Total events	115		247			

Heterogeneity: $\chi^2 = 10.35$, 8 d.f., $P = 0.24$; $I^2 = 23\%$

Test for overall effect: $Z = 8.21$, $P < 0.00001$



b

Study or subgroup	NOSE Mean	NOSE s.d.	NOSE Total	LAP Mean	LAP s.d.	LAP Total	Weight (%)	Mean difference IV, Fixed, 95% c.i.
Ding *et al.*[26]	3.8	1.1	43	4.4	1.4	43	13.4	−0.60 (−1.13, −0.07)
Zhou *et al.*[31]	3.9	0.6	52	4.1	0.9	52	43.9	−0.20 (−0.49, 0.09)
Park *et al.*[33]	7.05	4.31	138	8.61	5.65	138	2.7	−1.56 (−2.75, −0.37)
Kim *et al.*[36]	3.8	1	58	4.1	1.2	58	23.5	−0.30 (−0.70, 0.10)
Park *et al.*[38]	4.6	0.9	34	5	1.1	34	16.6	−0.40 (−0.88, 0.08)
Total (95% c.i.)			325			325	100.0	−0.35 (−0.54, −0.15)

Heterogeneity: $\chi^2 = 5.95$, 4 d.f., $P = 0.20$; $I^2 = 33\%$

Test for overall effect: $Z = 3.49$, $P = 0.0005$

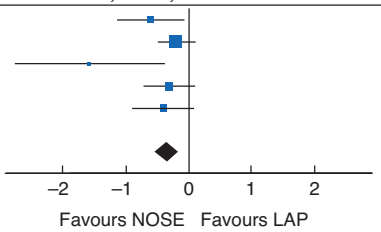


Fig. 6 Forest plot of secondary outcomes
a Additional use of analgesia after surgery. **b** Time to resume regular diet. LAP, laparoscopy; NOSE, natural orifice specimen extraction.

Sensitivity analysis

Sources of heterogeneity were assessed by conducting sensitivity analysis based on the specimen extraction site (studies that assessed transvaginal specimen extraction and those with a mix of both transvaginal and transanal specimen extraction were excluded); sample size (analysis was restricted to publications with the sample size of each intervention arm being more than 35); methodological quality of the studies (restricted to RCTs). As there were only three RCTs in this meta-analysis that did not assess all of the study outcomes, further sensitivity analysis that excluded non-randomized studies with moderate and high risk of bias was performed.

Most of the primary and secondary outcomes remained consistent across the different types of analysis (*Table S6*), except for lymph node collection, additional analgesia, and operating time.

Publication bias

Visual inspection of funnel plots of the primary outcomes was performed, when more than 10 studies were included in the analysis. Funnel plots for postoperative complications, lymph node collection, and cancer recurrence show that all included studies are within the 95 per cent confidence interval. Additionally, the scatter points are almost symmetrically distributed in the inverted funnel plots (*Fig. S2*).

Discussion

Over the past two decades, refinement of laparoscopy has led to the development of NOSE. Despite the increasing recognition of this emerging technique in benign conditions, its safety and oncological benefits in CRC were still questionable.[39,40] Based on recent publications of NOSE, this meta-analysis demonstrated the oncological safety and efficacy of NOSE compared with transabdominal specimen extraction in laparoscopic surgery for CRC.

Patient morbidity is an efficient measure to assess the safety of a new procedure. In this meta-analysis, the overall postoperative complications of NOSE were significantly lower when compared with LAP. This can be attributed to the use of the natural orifice for specimen extraction, obviating the mini-laparotomy incision and its associated complications. In fact, this meta-analysis showed that patients in the NOSE group had a significant decrease in wound infection rates compared with the LAP group.

Bacterial contamination of the peritoneal cavity is a common occurrence in conventional laparoscopic colorectal resections. Concerns arise regarding the breach in peritoneal sterility that occurs in NOSE.[41] Despite a few studies showing that higher peritoneal contamination and positive bacterial growth in peritoneal fluid is found in NOSE compared with LAP, there were no significant differences in clinical outcomes (peritoneal infection or infection-related complications)[42,43]. Pooled results of this meta-analysis demonstrated a significant decrease in wound infections in patients who underwent the NOSE procedure. Apart from attributing this to increased precautionary measures, it is also a result of the avoidance of the mini-laparotomy wound in NOSE. The decrease in wound infections may subsequently lead to a reduction in wound-related complications. There was no statistically significant difference in the rate of intraperitoneal infection and intrabdominal abscess formation in NOSE when compared with LAP; however, all other infectious complications, including

pneumonia, urinary tract infection, and fistula formation were comparable between both groups. The NOSE and LAP techniques did not differ in the frequency of other major and possible life-threatening complications, including anastomotic leak, postoperative haemorrhage, venous thromboembolism, and ileus. Additionally, no significant difference in the occurrence of incisional hernias and reoperation was observed.

The postoperative pathology outcomes are also a reflection of surgical safety and quality[44,45]. Radical surgery with curative intent involves resection of the tumour and its associated lymphatics, aiming to obtain a tumour-free margin. This meta-analysis showed no significant difference between NOSE and LAP groups in terms of proximal and distal resection margins.

Multiple studies have shown that there is a direct correlation between the number of lymph nodes collected and those identified with metastasis. To obtain a correct diagnosis of N0 in around 90 per cent of patients, the College of American Pathologists established that at least 12 lymph nodes should be collected to declare a patient free from lymph node metastasis[46,47]. All included studies in this meta-analysis collected more than 12 lymph nodes, which is the recommended requirement (mean dissected lymph nodes of 17.8 in NOSE and 17.2 in LAP). This is comparable to a previous meta-analysis which was conducted on 1787 patients with sigmoid and rectal tumours, whereby the mean number of dissected lymph nodes was found to be 15.2 and 16.3 for the NOSE and LAP groups respectively[7].

This meta-analysis sought to address long-term oncological safety in the application of NOSE. The theoretical possibility of tumour seeding may occur because of the manipulation during specimen extraction via narrow natural orifice; compromising oncological safety[4,48] and influencing the incidence of local recurrence and survival rates[49]. This meta-analysis showed that the total cancer recurrence as well as local 5-year recurrence rate in the NOSE group were comparable to the LAP group. Additionally, no significant difference in the 5-year disease-free survival and overall survival was demonstrated. These results suggest that the long-term curative effect of NOSE is comparable to transabdominal specimen extraction, and safe for use in CRC.

The benefits of NOSE have also been reflected in the secondary outcomes of this meta-analysis. The pooled data on 16 studies showed a statistically significant decrease in intraoperative blood loss in NOSE compared with the LAP group. This advantage is possibly secondary to the avoidance of the mini-laparotomy wound and the maintained pneumoperitoneum pressure in NOSE, suppressing capillary and venous bleeding[50,51]. Owing to the small incisions in minimally invasive surgery, patients who underwent NOSE experienced significantly less postoperative pain throughout the postoperative interval from days 1 to 5 compared with the mini-laparotomy in conventional laparoscopy. Consistent with this finding, this meta-analysis shows a decreased need for additional analgesia after surgery. The outcome of this meta-analysis agrees with two previous meta-analyses conducted in this field, both of which were performed in patients with benign and malignant tumours[5,7].

Patients undergoing abdominal surgery tend to develop an interval of impaired gastrointestinal motility or postoperative ileus. Being minimally invasive, this meta-analysis showed that NOSE results in improved recovery of gastrointestinal function as demonstrated by earlier first passage of flatus/defaecation and resumption to regular diet. This significantly contributes to decreased patient morbidity and it is also an important determinant of the patient's duration of hospital stay[52]. Consistent with this finding and the overall decrease in morbidity, the results from the pooled analysis revealed accelerated recovery and a significant shorter duration of hospital stay in patients who underwent NOSE. Additionally, the small incisions in NOSE compared with the mini-laparotomy in conventional laparoscopy have resulted in improved aesthetic outcomes in NOSE, as demonstrated by the higher cosmetic score and improved patients' satisfaction with the appearance of the abdominal wall. This corresponds to the findings of a previous meta-analysis performed on 1437 patients with CRC[6].

Consistent with previous findings[8], this meta-analysis demonstrated prolonged operating times to perform NOSE compared with conventional laparoscopy. The acquaintance with a relatively new surgical technique as well as intracorporeal suturing and anastomosis might have been a possible factor contributing to prolonged operating time[35,53,54]. The results of the subgroup analysis here reported, demonstrated a statistically significant subgroup effect when assessing the specimen extraction site in terms of intraoperative blood loss and distal resection margin; however, it should be noted that the transvaginal group was underpowered. Meta-regression has also identified significant relationships between patient characteristics (BMI and ASA grade I–III) and treatment effect, but these cannot be regarded as a proof of causality. Results of sensitivity analysis remained consistent to overall outcomes of the primary analysis, further supporting the reliability of our findings.

Limitations were present in this meta-analysis, which require further consideration. Most of the included studies are non-randomized studies, with some of these having small sample size and methodological concerns, hence influencing the power of the pooled results. It should be noted that in addition to the different patient and tumour characteristics, the studies were performed by different surgical teams, and this might have led to differences in the skill of the surgeon, operating technique, and outcome measures among the studies. The limited number of available studies for some of the outcomes might have restricted the sensitivity and subgroup analysis, compromising the power of the statistical analysis. Additionally, as publication bias was assessed only with visual inspection of funnel plots without any formal statistical testing, this could result in assessment bias. As most of the studies were conducted in Asia, it is unclear whether the results of this meta-analysis can be generalized to other populations that may have different patient and tumour characteristics as well as healthcare systems. Subgroup analysis restricted to the pathology site (right and left side) was not performed as only two studies assessed right-sided tumours, both pertaining to the transvaginal subgroup. This is a significant source of heterogeneity that is likely to have an impact on the overall results of this meta-analysis. Moreover, in this meta-analysis, given the limited number of studies, transrectal and transanal resections were considered as one group in subgroup analysis, which might have resulted in bias. In this meta-analysis, only few of the included studies reported the HR and the method of Tierney[17], using data extraction from survival curves, was used for analysis. This may have led to estimation bias. Additionally, the included studies reported considerable variation in the length of follow-up interval. Given the due importance of recurrence rates and survival evaluation, further longitudinal studies are needed to validate the findings.

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Disclosure. The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The datasets during the present study are available from the corresponding author on reasonable request.

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