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Original Article

'4-Check' protocol for intraoperative anastomotic assessment during transanal total mesorectal excision: retrospective cohort study

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Abstract

Background: Anastomotic leakage is a major complication following rectal cancer surgery. The primary aim of this study was to investigate the efficacy of a protocol based on a quadruple intraoperative anastomotic assessment (4-Check) during transanal total mesorectal excision (TaTME).

Methods: Patients who underwent TaTME for rectal cancer with primary anastomosis were reviewed and divided into two groups: before (pre-4-Check: April 2015 - April 2019) and after the implementation of the 4-Check protocol (May 2019 - May 2022). This protocol consisted of a multimodal anastomotic integrity assessment, including indocyanine green-evaluation of colonic stump and intraluminal anastomosis perfusion, a reverse air leak test and anastomotic doughnuts assessment. The primary outcome was incidence of clinical and/or radiological anastomotic leakage. The secondary outcome included intraoperative anastomosis defects and repairs and 30-day complication rate. Propensity score matching and multivariable analyses were performed.

Results: Of 186 patients, 160 were selected: 86 patients in the pre-4-Check and 74 in the 4-Check group. After propensity score matching, there was no difference in postoperative anastomotic leakage (pre-4-Check *versus* 4-Check: 11.1 per cent *versus* 7.4 per cent; $P = 0.50$). However, in the 4-Check group, the intraoperative detection of defects and repairs was significantly increased ($P = 0.03$), and the number of complications was reduced (pre-4-Check *versus* 4-Check: 33.3 per cent *versus* 9.3 per cent, $P = 0.004$). Multivariable analyses confirmed that the use of the 4-Check protocol, the detection of anastomotic defects and increased albumin levels were associated with a reduced number of complications.

Conclusion: The 4-Check protocol allowed the intraoperative detection and repair of anastomotic defects. Anastomotic leakage rates were not reduced; however, 30-day complication rates were lower after implementation of this protocol.

Introduction

Anastomotic leakage (AL) is still one of the major complications following colorectal resection, with a prevalence of approximately 10 per cent after rectal cancer surgery[1]. AL has been associated with increased health-related costs, an increased risk of permanent stoma[2] and worse long-term oncological outcomes[3].

Although there are several definitions of AL, one of the most commonly used is the one provided by the International Study Group of Rectal Cancer: a '*defect of the intestinal wall integrity at the colorectal or coloanal anastomotic site (including suture and staple lines) leading to a communication between the intra and extraluminal compartment*[4]'.

The pathogenesis of AL is related to modifiable and non-modifiable factors that can have an impact on anastomotic healing, including patient, cancer, and operative factors[5]. In 2016, the Association of Surgeons of Great Britain and Ireland (ASGBI) guidelines highlighted the importance of promptly identifying an anastomotic defect. Technical defects are usually excluded by inspection of the anastomotic rings (doughnuts) and intraoperative leak tests. This test consists of air insufflation into the anastomosis after filling the pelvis with saline solution. If there is a defect in the anastomosis, bubbles are noticed in the pelvis[6] and the technical defect can be repaired through anastomotic resuturing; however, the utility of this technique alone is controversial[7].

Recently, a 'reverse test' has been suggested, involving transanal assessment of the anastomosis[8]. This is in addition to multiple other techniques including near-infrared (NIR) indocyanine green (ICG)-induced fluorescence angiography (FA), to enable a real-time intraoperative perfusion assessment. NIR ICG FA assessment of colorectal anastomoses has been shown to be associated with a lower rate of anastomotic leak and complications. However, sole assessment with ICG-assessed changes in the surgical resection might be associated with a higher risk of AL[9].

In 2019, a quadruple assessment of colorectal anastomosis[10] including anastomotic doughnuts assessment, air leak test and

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the ICG evaluation of the colonic stump/anastomotic mucosa was described. One of the technical advantages of the transanal total mesorectal excision (TaTME) approach over other mini-invasive procedures is the use of a transanal platform that allows for the assessment and intraluminal repair of any intraoperatively detected defects. After the introduction of TaTME procedures for low rectal cancers at the author's institution, anastomotic assessment was implemented using the combination of all perfusion/mechanical tests. However, in comparison to the quadruple assessment, in this protocol the mechanical integrity of the anastomosis was tested through a reverse air leak test. The reverse approach offers the advantage of precise localization of the anastomotic defect, thanks to direct visualization of the anastomotic suture during the evaluation.

The primary aim of this study was to investigate the efficacy of a systematic protocol (4-Check) for intraoperative anastomotic assessment during TaTME in decreasing AL rates. The secondary aims were the reduction of morbidity, hospital stay and time to stoma closure.

Methods

This is a retrospective controlled study pre- and post-implementation of the 4-Check protocol, which was designed and reported according to the STROBE criteria[11] (Fondazione Policlinico Universitario A. Gemelli IRB approval ID 5417).

Study population

Since its introduction at the author's unit (Fondazione Policlinico Universitario A. Gemelli in Rome), TaTME has been the technique of choice for patients with low and mid rectal cancers (1–6 cm and 7–11 cm from the anorectal junction, respectively), as previously reported[12].

All consecutive adult patients of either sex who underwent TaTME with primary colorectal or coloanal anastomosis with or without loop ileostomy or colostomy between April 2015 and September 2022 were eligible for enrolment.

The exclusion criteria were benign diseases (e.g., inflammatory bowel disease), absence of primary anastomosis (e.g., Hartmann's/Miles procedure), and the use of other reconstruction techniques (e.g, J pouch).

The management of all rectal cancer patients is discussed weekly at multidisciplinary team meetings. Patients with cT3–cT4a N0 disease or those staged cTN+ are usually treated with neoadjuvant chemoradiotherapy (NAD), consisting of 4 weeks of radiotherapy (total dose of 56 Gy) plus concomitant 5-fluorouracil, followed by delayed surgery after at least 6 weeks. Patients unfit for chemotherapy are usually scheduled for short-term radiotherapy (total dose of 25 Gy) followed by immediate or delayed surgery.

All clinical (age, sex, smoking habits, BMI, Charlson Index, use of anti-latelt/anti-coagulant drugs, preoperative albumin plasma level), cancer-related (clinical and pathological stages including mesorectal fascia [MRF] involvement, distance from the anorectal junction [ARJ] measured on preoperative MRI, use of neoadjuvant treatment) and operative features (operative time, type of anastomosis and staplers, intraoperative anastomotic assessment, detection of anastomotic defects and anastomotic intraoperative repairs) were collected in a prospectively maintained database and reviewed for the purpose of the analyses.

Finally, all selected patients were categorized into two groups according to the intraoperative anastomotic assessment, before (pre-4-Check) and after the introduction of the (4-Check) protocol.

Procedures

From April 2015 to April 2019 (pre-4-Check), the integrity of the anastomosis was assessed intraoperatively through the examination of both the colonic/rectal 'doughnuts' and air leak test. The air leak test was performed by filling the pelvis with saline solution to the level of the anastomosis during a transabdominal anastomotic evaluation. Air was insufflated through a tube positioned into the rectum, while the proximal colon was clamped. The presence of free extraluminal bubbles within the fluid was regarded as the sign of a breach in the anastomosis, and in this case, the Gel Point path device (Applied Medical, CA, USA) was reinserted for anastomotic evaluation. The area that was suspected to have dehiscence was located via a transanal approach and oversewn using a V-lock or a Vicryl 3/0 suture. The test was then repeated to reassess the leak site treatment to check the absence of bubbles (negative test).

In May 2019, a systematic protocol for anastomotic integrity assessment was introduced (4-Check). The test combines four items: extraluminal (serosal) evaluation of proximal colon perfusion based on a semiquantitative assessment of NIR-ICG-induced FA; endoluminal (mucosal) anastomotic evaluation perfusion based on a semiquantitative assessment of NIR-ICG-induced fluorescence angiography; reverse air leak tests; and anastomotic doughnut assessment (*Fig. 1*).

NIR-ICG-induced FA is conducted by intravenously administering a bolus of 3.75–7.5 mg of ICG (0.2 mg/kg) and the proximal colonic stump is intra-abdominally evaluated using a fluorescence imaging system. Following completion of the anastomosis, a second bolus is administered. The anastomosis is visualized and scored for any perfusion defect by the transanal insertion of the system. A positive test is defined as a 'poor' (meaning non-uniform distribution of fluorescence) or 'absent' (no fluorescence) signal at the serosal or mucosal level[13]. A 'good' perfusion (meaning uniform distribution of fluorescence) was recorded as a negative test.

The reverse air leak test consists of filling the rectum with a small amount of saline solution during transanal visualization of the anastomotic line through a circular anal dilator. In the presence of any anastomotic defect, bubbles are identified when they are seen leaking in between the suture line due to the passage of CO_2 from the pneumoperitoneum. In the case of a positive reverse air leak test, the leak area is identified, and buttressed sutures with V-lock or Vicryl 3/0 are placed. The test is repeated to reassess the leak site treatment[6,8].

Outcomes

The study objective was to evaluate the efficacy of the 4-Check protocol, and the primary outcome was the overall incidence of clinical and/or radiological AL[4]. Since 2015, all patients have been enrolled in an enhanced recovery after surgery (ERAS) programme[14]. Clinical ALs were diagnosed by abdominal contrast-enhanced CT scans (including pelvic collections) or intraoperative findings, in patients who underwent reoperation. All patients with protective stomas routinely underwent an X-ray contrast-enhanced enema before stoma closure 6 weeks following the primary surgery, meaning asymptomatic ALs were recorded. The overall incidence of intraoperative anastomosis defects and repairs (defined as anastomotic buttressed sutures), 30-day complications (Clavien–Dindo Classification[15] and

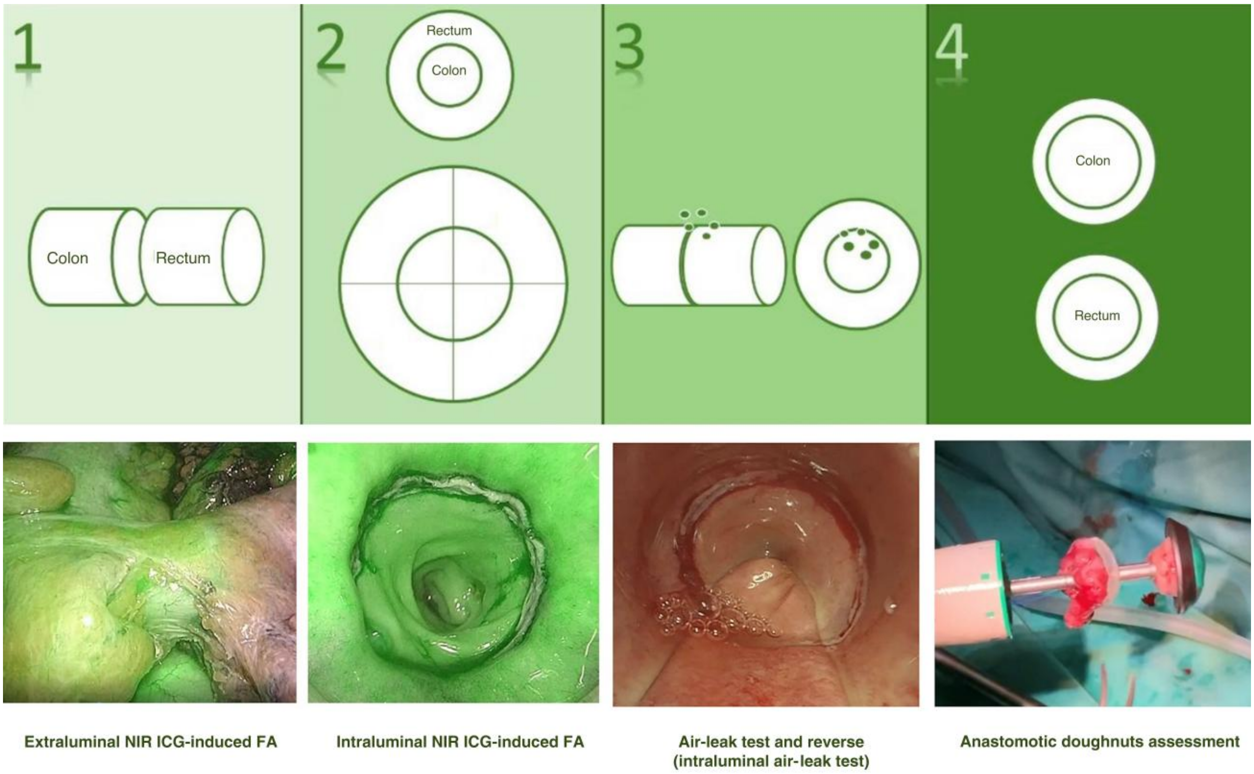

Fig. 1 4-Check diagram

(1) Extraluminal (serosa) evaluation of the proximal colon perfusion based on a semiquantitative assessment of the NIR ICG-induced FA; (2) intraluminal (mucosal) anastomotic evaluation of perfusion, based on a semiquantitative assessment of the NIR-ICG-induced FA; (3) reverse air leak tests; and (4) anastomotic doughnuts assessment. NIR, near infrared; ICG, indocyanine green; FA, fluorescence angiography.

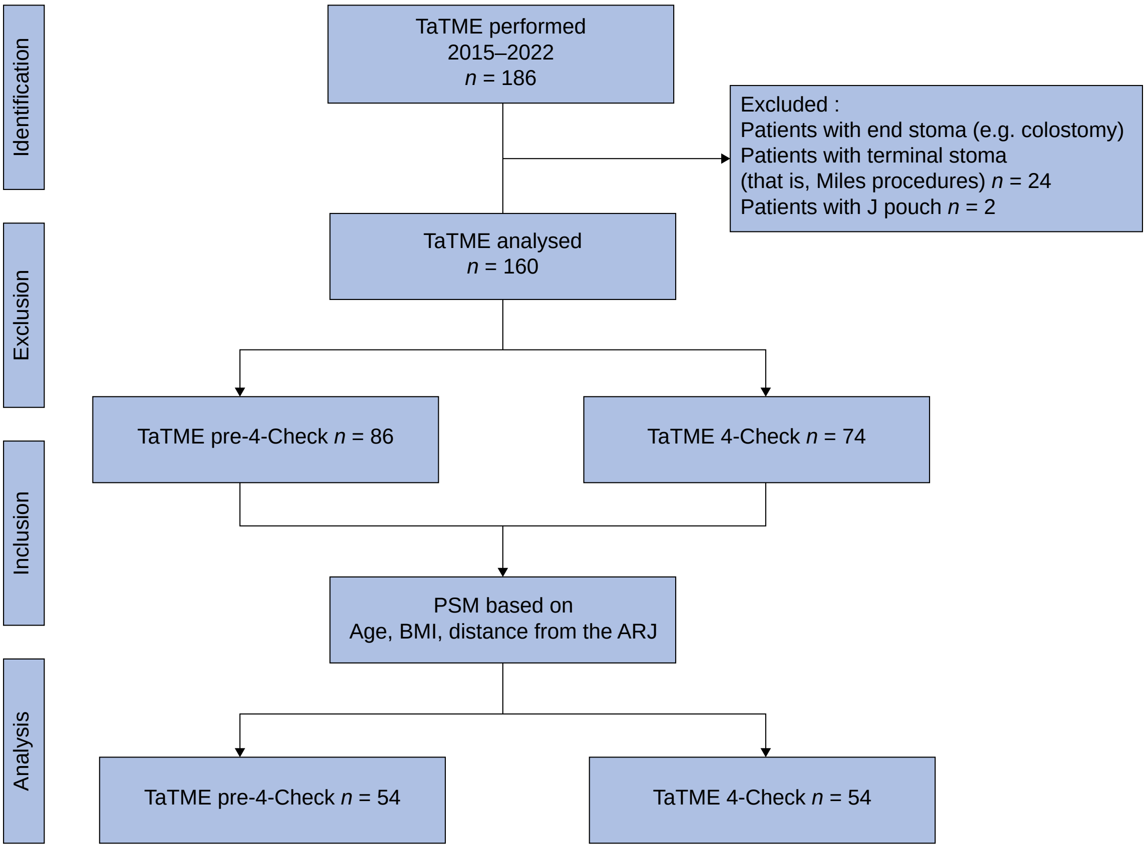

Fig. 2 Study flowchart

ARJ, anorectal junction; PSM, propensity score matching; TaTME, transanal total mesorectal excision.

Comprehensive Complication Index[16], CCI), postoperative length of stay (days), and time to stoma closure (months) were considered as secondary outcomes. The incidence of permanent stomas (defined as the absence of stoma reversal due to AL) was recorded but not selected as an outcome of interest due to the small number of events.

Statistics

Preliminary descriptive analyses were performed considering the distribution (mean(s.d.), median, or interquartile range) and frequencies of the variables (percentages). The two groups (pre-4-Check and 4-Check) were compared using the Mann–Whitney test, *t*-test, and Pearson's chi-square test. Propensity score matching (PSM) was performed to reduce any group imbalances based on the variables that showed high Gini mean difference (GMD) and that could favour the pre-treatment group. Therefore, through library 'MatchIt' in R, the matching specification considering these parameters: 'full' method, 'glm' distance, link 'probit' and 0.2 calliper was set and the imbalance reduced considering the lowest standardized mean difference (SMD; <0.1). A post-hoc power calculation was conducted on PSM analysis using the PWR package. The outcomes of interest were also studied using a generalized linear model (GLM). Finally, another logistic model was performed with the leave one out cross-validation (LOOCV) resampling technique on 100 models to implement the study population, estimating variance over the entire sample. All statistical analyses were two-tailed and performed using IBM SPSS Statistics 29.0.0.0 (241) software and R (4.1.2) (https://cran.r-project.org) with statistical significance set at a $P \leq 0.05$.

Results

Study population

Of 186 patients who underwent TaTME for rectal cancer, 160 were selected: 86 patients pre-4-Check and 74 treated using the 4-Check protocol. Twenty-six were excluded: 24 patients because of non-restorative rectal surgery and two patients because of J pouch reconstruction (*Fig. 2*). Demographic, clinical, oncological, and operative features of the patients are outlined in *Table 1*.

Patients who had the 4-Check protocol had a greater Charlson Index ($P = 0.004$) and lower preoperative albumin levels (*Table 2*). These patients were also younger (median age: 65.4 years 4-Check *versus* 68.8 years pre-4-Check; $P < 0.01$) with lower BMI ($P < 0.01$), and their tumours were located more proximally (median distance from the ARJ pre-4-Check *versus* 4-Check group: 53 mm *versus* 70 mm; $P < 0.01$; *Table 2*).

AL occurred in 18 patients. In five patients (four patients pre-4-Check and one patient 4-Check), the ALs presented with clinical signs and symptoms and required emergency surgery. In 13 patients (8 pre-4-Check and 5 4-Check) the ALs were asymptomatic, and there were documented radiological findings at the time of the routine 6-week X-ray enemas before stoma closure.

Propensity score matching

PSM analysis was performed to correct the distribution of age, BMI, and ARJ distance, selecting 54 patients in each group (*Fig. S1* and *Table S1*). AL occurred in six patients (11.4 per cent) in the pre-4-Check group and four patients (7.4 per cent) in the 4-Check group (*Table 3*). A post-hoc power calculation demonstrated a power ($1 - \beta$) of 0.86, with an α error of 0.05 and an effect size of 0.3.

Table 1 Clinical and pathological features of the case series

Feature	
Age (years), median (i.q.r.)	69.0 (61.0–76.0)
Sex, *n* (%)	
Female	63 (39.4%)
Male	97 (60.6%)
M/F	1.5
Smoking habits, *n* (%)##	
Yes	24 (15.0%)
No	60 (37.5%)
Ex-smoker	52 (32.5%)
BMI, median (i.q.r.)	24.8 (22.9–27.6)
Charlson index, median (i.q.r.)*	3 (2.0–4.0)
Anticoagulant or antiplatelet drug use, *n* (%)	
Yes	42 (26.3%)
No	118 (73.7%)
Albumin (g/dl), median (i.q.r.)	40.0 (38.0–42.0)
cT4-Mesorectal fascia involvement, *n* (%)	
Yes	40 (25.0%)
No	120 (75.0%)
Neoadjuvant treatment, *n* (%)	
Yes	105 (65.6%)
No	55 (34.4%)
Distance from the anorectal junction (mm), median (i.q.r.)#,¶	60.0 (45.0–78.5)
Operative time (min), median (i.q.r.)	290.0 (253.8–340.0)
Anastomosis, *n* (%)	
Mechanical—circular 29 mm	33 (20.6%)
Mechanical—circular 31 mm	2 (1.3%)
Mechanical—circular 33 mm	116 (72.5%)
Manual—coloanal	9 (5.6%)
Anastomosis check: detection of anastomotic defects, *n* (%)	
Yes	20 (12.5%)
No	140 (87.5%)
Anastomosis check: intraoperative repair, *n* (%)	
Yes	10 (6.2%)
No	150 (93.8%)
Postoperative anastomotic leak, *n* (%)	
Yes	18 (11.3%)
No	142 (88.7%)
30-day postoperative complications, *n* (%)†	
Clavien 0	117 (73.1%)
Clavien 1	26 (16.3%)
Clavien 2	10 (6.3%)
Clavien 3	5 (3.1%)
Clavien 4	1 (0.6%)
Clavien 5	1 (0.6%)
Terminal stoma‡,§,**	
Yes	7 (4.4%)
No	119 (74.3%)
Time to stoma closure (months), median (i.q.r.)	6.5 (3.4–10.2)
Length of hospital stay (days), median (i.q.r.)	5.0 (4.0–7.0)

##Missing data: 24 (15.0%); *missing data: 1 (0.6%); #measured on MRI; ¶missing data: 4 (2.5%); †complications according to Clavien classification; ‡stoma closure not performed due to anastomotic leak; §data calculated on 126 patients; **missing data: 34 (21.3%).

The intraoperative detection of anastomotic defects was registered in four patients (7.4 per cent) in the pre-4-Check group and in 12 patients (22.2 per cent) in the 4-Check group ($P = 0.03$).

Intraoperative reinforcement/repair of the anastomosis was performed in one patient (1.8 per cent) and seven patients (12.9 per cent) in the pre-4-Check and 4-Check groups, respectively ($P = 0.02$). No statistically significant difference was documented in the operative time between the two groups. Postoperative complications occurred in 18 patients (33.3 per cent) in the pre-4-Check group and in five patients (9.3 per cent) in the

Table 2 Demographic, clinical and oncological features in pre-4-Check *versus* 4-Check groups before propensity score matching (pre-PSM) and after (post-PSM)

	Pre-PSM		P value	OR** (95% c.i.)	Post-PSM		P value	OR** (95% c.i.)
	Pre-4-Check (*n* = 86)	4-Check (*n* = 74)			Pre-4-Check (*n* = 54)	4-Check (*n* = 54)		
Sex, *n* (%)								
Female	30 (34.8%)	33 (44.5%)	0.27¶	1.5(0.7–2.8)	19 (35.2%)	23 (42.6%)	0.43¶	1.3(0.6–2.9)
Male	56 (65.2%)	41 (55.5%)			35 (64.8%)	31 (57.4%)		
Age (years), median (i.q.r.)	68.8 (62.04–76.5)	65.4 (59.0–75.0)	<0.01#	1.5 (0.8–2.9)	66.0 (59.0–74.5)	69.0 (61.0–76.8)	0.52#	0.7 (0.3–1.5)
Smoking habits, *n* (%)								
Yes	13 (15.2%)	11 (14.8%)	0.73¶	0.7(0.2–1.9)	10 (18.5%)	9 (16.6%)	0.67¶	0.9(0.3–3.1)
No	37 (43.0%)	23 (31.1%)			17 (31.5%)	15 (27.8%)		
Ex-smoker	33 (38.3%)	19 (25.7%)		1(0.5–2.3)	24 (44.4%)	15 (27.8%)		1.4(0.5–3.6)
Missing data	3 (3.5%)	21 (28.4%)			3 (5.6%)	15 (27.8%)		
BMI, median (i.q.r.)	24.9 (23.2–28.1)	24.4 (22.2–27.4)	<0.01#	1.2 (0.6–2.3)	24.2 (23.1–26.9)	24.9 (22.8–27.3)	0.58#	0.7 (0.3–1.5)
Charlson index, median (i.q.r.)	2 (1–3)	4 (2–6)	0.004#	0.1 (0.07–0.3)	2 (2–3)	4 (2–6)	≤0.001#	0.06 (0.02–0.1)
Anticoagulant or antiplatelet drug use, *n* (%)								
Yes	28 (32.6%)	14 (18.9%)	0.07¶	2(1–4)	14 (25.9%)	12 (22.3%)	0.20¶	1.2(0.4–3.0)
No	58 (67.4%)	60 (81.1%)			40 (70.1%)	42 (77.7%)		
Albumin (g/dl), median (i.q.r.)	40 (38–42)	40 (38–41)	<0.01#	0.9 (0.5–1.8)	40 (38–42)	40 (38–42.8)	0.99#	0.8 (0.3–1.8)
cT4–Mesorectal fascia involvement, *n* (%)								
Yes	23 (26.7%)	17 (22.9%)	0.71¶	1.2(0.6–2.6)	20 (37.0%)	12 (22.3%)	0.92¶	2.1(0.8–4.8)
No	63 (73.2%)	57 (77.1%)			34 (63.0%)	42 (77.7%)		
Neoadjuvant treatment, *n* (%)								
Yes	52 (60.4%)	53 (71.6%)	0.18¶	0.61(0.31–1.18)	35 (64.8%)	39 (72.2%)	0.40¶	0.7(0.3–1.6)
No	34 (39.6%)	21 (28.4%)			19 (35.2%)	15 (27.8%)		
Distance from the anorectal junction (mm)*, median (i.q.r.)	53.0 (40.0–70.0)	70.0 (51.2–0.0)	<0.01#	0.3 (0.1–0.5)	60 (50–75)	65 (50–80)	0.57#	0.7 (0.3–1.5)
Anastomosis, *n* (%)								
Mechanical—circular	81 (94.2)	70 (94.6%)	0.9¶	0.9(0.2–3.7)	52 (96.3%)	51 (94.4%)	1¶	1.4(0.2–13.2)
Manual—coloanal	5 (5.8%)	4 (5.4%)			2 (3.7%)	3 (5.4%)		

*Measured on MRI; ¶chi-square test; #Mann–Whitney test; **OR are referred to the upper cut-off bound. PSM, propensity score matching.

4-Check group ($P = 0.004$). The length of hospital stay was similar in the two groups, while the median time for stoma reversal was 8.8 months (IQR 4.9–11.8) in the pre-4-Check group and 5.8 months (IQR 2.9–9.1) in the 4-Check group ($P = 0.04$). Reoperation rate was 1 per cent in the pre-4-Check group *versus* 1.8 per cent in the 4-Check group (1 *versus* 2 cases, $P = 0.56$).

A GLM was performed on the matched population to evaluate the association between clinical variables and postoperative complications. The analysis demonstrated that postoperative complications (assessed through the Clavien score) were associated with low levels of serum albumin ($P = 0.04$, β: −0.1, 95 per cent c.i. −0.2 to 0.008, OR 0.8), the pre-4-Check group ($P < 0.01$, β: 1.5, 95 per cent c.i. 0.4 to 2.8, OR 4.7) and the detection of anastomotic defects ($P = 0.02$, β:1.7, 95 per cent c.i. 0.3 to 3.3, OR 5.7) (Table S2). Use of neoadjuvant treatment was associated with fewer postoperative complications.

After LOOCV resampling on 100 models, the association between postoperative complications and serum albumin levels, the pre-4-Check group, and the intraoperative detection of anastomotic defects was confirmed with P values of 0.04, 0.01, 0.02, and 0.01, respectively.

This trend was confirmed when analysing CCI (Table S3).

Discussion

The present study investigated the systematic and combined use of perfusion/technical tests (the 4-Check protocol) to intraoperatively identify and possibly repair high-risk colorectal anastomosis to reduce the incidence of postoperative complications, such as AL. The 4-Check protocol increased the intraoperative detection of anastomotic defects and allowed for an increased number of anastomotic revisions, with a significant reduction in the rate of 30-day postoperative complications.

The protocol gave the opportunity to identify high-risk colorectal anastomoses and modify surgical interventions at the time of the index operation with the goal of minimizing adverse events. Despite progress in the technical aspects and clinical patient management, rectal surgery is still burdened by complications such as infections, bleeding, and AL.

AL increases patient morbidity, often requiring additional therapeutic and/or surgical interventions. This leads to longer hospital stays and increased costs. It reduces quality of life and is related to an increased rate of permanent stoma[17]. Risks related to AL are not limited to the perioperative period, it is linked to worse oncological outcomes, and the mortality rate

Table 3 Primary and secondary outcomes in pre-4-Check *versus* 4-Check groups before propensity score matching (pre-PSM) and after (post-PSM)

	Pre-PSM		P value	OR** (95% c.i.)	Post-PSM		P value	OR** (95% c.i.)
	Pre-4-Check (*n* = 86)	4-Check (*n* = 74)			Pre-4-Check (*n* = 54)	4-Check (*n* = 54)		
Operative time (min), median (i.q.r.)	289 (256–321)	296 (252–349)	<0.01#	0.7 (0.4–1.4)	293 (265–321)	297 (250–340)	0.95#	0.8 (0.4–1.8)
Anastomosis check: detection of anastomotic defects, *n* (%)								
Yes	5 (5.8%)	15 (20.3%)	0.01¶	0.2 (0.07–0.6)	4 (7.4%)	12 (22.2%)	**0.03¶**	0.2 (0.07–0.9)
No	81 (94.2%)	59 (79.3%)			50 (92.6%)	42 (77.8%)		
Anastomosis check: intraoperative repair, *n* (%)								
Yes	1 (1.1%)	9 (12.2%)	0.01¶	0.09 (0.003–0.5)	1 (1.8%)	7 (12.9%)	**0.03¶**	0.1 (0.005-0.8)
No	85 (98.9%)	65 (87.8%)			53 (98.2%)	47 (87.1%)		
30-day postoperative complications, *n* (%)†								
C0	54 (62.7%)	63 (85.1%)	0.002¶	3.3 (1.5–7.5)	36 (66.7%)	49 (90.7%)	**0.002¶**	4.7 (1.6–15.7)
C1–5	32 (37.3%)	11 (14.9%)			18 (33.3%)	5 (9.3%)		
30-day postoperative complications, *n* (%)†								
C0	54 (62.8%)	63 (85.1%)	0.006¶	3.4 (1.5–8.4)	36 (66.7%)	49 (90.7%)	**0.004¶**	6.8 (2.1–32.6)
C1–2	27 (31.4%)	9 (12.2%)		2.7 (0.5–22.2)	16 (29.6%)	3 (5.6%)		1.3 (0.1–13.5)
C3–5	5 (5.8%)	2 (2.7%)			2 (3.7%)	2 (3.7%)		
Postoperative anastomotic leak, *n* (%)								
Yes	12 (13.9%)	6 (8.1%)	0.35¶	1.8 (0.6–5.5)	6 (11.1%)	4 (7.4%)	0.50¶	1.5 (0.4–6.6)
No	74 (86.1%)	68 (91.9%)			48 (88.9%)	50 (92.6%)		
Terminal stoma, *n* (%)‡,§								
Yes	5 (5.8%)	2 (2.7%)	0.82¶	0.6 (0.07–3.1)	2 (3.7%)	1 (1.8%)	0.35¶	
No	71 (82.6%)	48 (64.8%)			44 (81.5%)	39 (72.3%)		1.6 (0.1-53.5)
Missing data	10 (11.6%)	24 (32.4%)			8 (14.8%)	14 (25.9%)		
Time to stoma closure (months), median (i.q.r.)	7.0 (4.1–11.1)	5.0 (2.9–8.8)	<0.01#	2.7 (1.3–5.9)	8.8 (4.9–11.8)	5.8 (2.9–9.1)	0.04#	2.5 (1.0.-5.6)
Length of hospital stay (days), median (i.q.r.)	5 (4–7)	5 (4–6)	<0.01#	1.6 (0.8–3.1)	4.5 (4–7)	5 (4–5.7)	0.53#	1.6 (0.7–3.8)

†Complications according to Clavien classification; ‡stoma closure not performed due to anastomotic leak; §data calculated on 126 patients for the Pre-PSM group and on 86 patients for the post-PSM group; ¶Pearson chi-square test; #Mann–Whitney test; **OR are referred to the upper cut-off bound; bold indicates statistical significance. PSM, propensity score matching.

related to symptomatic anastomotic leak ranges from 6 per cent to 22 per cent[18].

AL risk increases from both modifiable and non-modifiable factors that can have an impact on anastomotic healing[19,20], including patient factors (sex, BMI, ASA score, tobacco use, preoperative radiation), cancer-related factors (diameter, distance from the anal verge, and stage)[20–22] and operative factors (level of anastomosis, multiple firing of staplers, intraoperative blood loss and operation time, suboptimal perfusion of the intestinal stumps, anastomotic technical defects)[5,20,21].

These last two elements have been proposed as the two most relevant issues that could have an impact on anastomotic healing[21,23]. Although several methods have been proposed to quantify perfusion, which are based on the timing and quantification of FA or on the intraoperative endoscopic evaluation of the mucosa, not all are reproducible in different settings. The utility and feasibility of NIR ICG-induced FA at the time of anastomosis creation has been recently documented and resulted in a change in the level of bowel resection in 11–13 per cent of cases[24].

This analysis reported a significant increase in intraoperatively detected anastomotic defects such as hypoperfusion areas or anastomotic disruptions when routinely performing 4-Check. In this series, the 4-Check group was also characterized by a significantly increased number of intraoperative anastomotic repairs, mainly buttressed sutures, after a positive leak test. In line with the literature, the multivariable analysis showed that low preoperative values of serum albumin, the presence of any anastomotic anomalies during the leak tests and an anastomotic assessment performed before the 4-Check implementation were independently associated with overall postoperative complications, including clinical or radiological AL.

The results reported in relation to neoadjuvant treatment are more difficult to explain. However, it should be noted that among patients who underwent neoadjuvant therapy, the great majority (95.2 per cent) had a protective stoma. It is possible that the presence of protective ostomy might be associated with fewer postoperative complications more than neoadjuvant treatment itself.

Defunctioning stoma remains the most widely used method to prevent symptomatic AL and to reduce the risk of sepsis. In the present analysis, an increased number of patients who underwent TaTME without a diverting stoma in the 4-Check group was reported (4 pre-4-Check *versus* 12 with 4-Check patients, $P = 0.015$). This result is not related to the surgeon's preferences, as all the procedures were performed by the same team, but some demographic features could have had a role in this choice (lower mean BMI and age in the 4-Check group). It is possible that increasing expertise and the possibility of a four-step multimodal anastomotic integrity assessment could have influenced the decision of whether to perform a diverting stoma. A lower number of defunctioning ostomies could result in considerable benefits for patients in terms of quality of life, reduced risk of stoma-related complications (prolapse, bowel obstruction, renal failure) and, above all, the need for a second surgery for stoma reversal.

This study has limitations. It is a retrospective study with lack of randomization, and the single-centre nature of the study precludes external validity. However, every element of the protocol assesses a specific characteristic responsible for the anastomotic integrity, with a complementary role. As they are all tested together, it is not possible to assess the individual impact of each intervention. The strengths of the study are the standardization of the assessment, by the same surgical team, with a documented learning curve[25], which makes the study population homogeneous. The study did not demonstrate a reduction in AL rates, possibly due to the relatively small sample size, and these results need to be assessed in higher-powered studies. The secondary outcomes are encouraging and promote the use of the 4-Check protocol to optimize the operative and postoperative management of patients undergoing TaTME for rectal cancer.

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Author contributions

Flavio Tirelli (Conceptualization, Data curation, Methodology, Writing—original draft), Laura Lorenzon (Conceptualization, Methodology, Supervision, Writing—review & editing), Alberto Biondi (Supervision, Validation, Writing—review & editing), Ilaria Neri (Conceptualization, Data curation, Methodology, Writing—original draft), Gloria Santoro (Data curation, Formal analysis, Methodology), and Roberto Persiani (Conceptualization, Methodology, Project administration, Writing—review & editing).

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at *BJS Open* online.

Data availability

The data that support the findings of this study are available on request from the corresponding author, A.B. The data are not publicly available due to privacy restrictions.

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