Inflammatory response after transanal total mesorectal excision

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ABSTRACT

INTRODUCTION: The advantages of transanal total mesorectal excision (taTME) would be a reduction of the hernia rate and surgical trauma. The present study reports data for patients undergoing taTME and compares the post-operative immune response in taTME with those of conventional laparoscopic surgery (CLS) and single-port laparoscopic surgery (SPLS).

METHODS: A comparative cohort study in patients with rectal cancer undergoing taTME. C-reactive protein (CRP) and white blood cell count (WBC) were measured pre-operatively and on post-operative days one, two, three and four.

RESULTS: A total of 40 patients were included in taTME, 20 patients in CLS and 20 in SPLS. Patients' demographics (except for clinical staging), R0 resection and post-operative complication rates were comparable. The length of abdominal incisio-n was significantly lower by taTME than by both SPLS and CLS ($p < 0.001$). Distant resection margin was shorter in the taTME group ($p < 0.01$), and the quality of specimen differed between groups ($p < 0.01$). CRP and WBC increased significantly in each group ($p < 0.05$), but there was no difference between the groups.

CONCLUSIONS: There is no difference in the inflammatory response in patients with rectal cancer undergoing taTME surgery compared with CLS and SPLS. We therefore conclude that the length/presence of abdominal incision does not further reduce the post-operative inflammatory stress response in minimally invasive procedures. The surgical trauma extends beyond the abdominal incision and depends on the intra-abdominal handling of the tissue.

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In recent decades, surgical strategy has developed towards a minimally invasive access to the abdomen. Compared with open surgery, minimally invasive surgery decreases systemic stress response, rate of post-operative complications, length of hospital stay, surgical site infection and pain, and improves cosmetics. Surgical trauma induces a systemic stress response in the immune system, autonomic nervous system and hypothalamic-pituitary axis [1, 2]. The magnitude of the inflammatory response is directly related to the extent of surgical trauma, and levels of inflammatory mediators are associated with clinical outcomes including post-operative pain, mobilisation and length of hospital stay [1, 3, 4]. Activation of the immune response is furthermore related to increased post-operative morbidity and mortality and ultimately causes an increased recurrence rate and poor prognosis in patients with malignant disease [2-5]. Transanal total mesorectal excision (taTME) has rapidly become an important surgical method and the overall specimen quality, margins and morbidity rates appear to be comparable with those seen in conventional rectum resection [5]. Furthermore, taTME allows the resected specimen to be removed through the anus, thereby avoiding an abdominal incision, which may hypothetically further reduce the surgical stress response.

In this study, we report data for patients undergoing taTME and compare the immune response, measured by white blood cell count (WBC) and C-reactive protein (CRP) in the post-operative phase of taTME with conventional laparoscopic surgery (CLS) and single-port laparoscopic surgery (SPLS).

METHODS

Between August 2013 and September 2016, patients who underwent taTME with anal extraction of the resected specimen for rectal cancer were included to explore the impact of abdominal incision on surgical stress response. Remaining patients were randomised to either CLS or SPLS. The corresponding results have previously been reported [6]. The preoperative work-up was performed in accordance with national Danish guidelines [7]. All patients were discussed at multidisciplinary colorectal cancer team meetings prior to surgery. The technical aspects of CLS and SPLS have been described previously [6]. Conversion from CLS to open procedure was defined if the suprapubic incision was enlarged more than what was necessary to extract the resected specimen [8, 9]. Conversion from SPLS was defined as the need for placement of one or more additional ports to assist the operation [10]. Conversion in the taTME group was defined as conversion to open surgery.

Patient characteristics and perioperative data were

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recorded prospectively. All procedures were performed by two certified senior consultant surgeons with long-standing experience in laparoscopic surgery. The same surgeon (OB) performed all SPLS and taTME procedures.

The blood samples were obtained preoperatively at room temperature (defined the same day as surgery) and on post-operative days one, two, three and four. Plasma CRP was measured by a particle-enhanced turbidimetric immunoassay (Cobas 6000, C501, Roche). Laboratory analyses were made immediately after blood sample preparation. The method was calibrated against the World Health Organization International Reference Preparation CRM 470. The detection limit of the assay was 0.3 mg/l with a measuring range up to 700 mg/l.

TABLE 1

Patient characteristics.

	SPLS (n = 20)	CLS (n = 20)	taTME (n = 40)	p-value
Age, median (range), yrs	69 (50-86)	73 (50-84)	67 (48-89)	0.18
Gender (female/male), n	12/8	12/8	14/26	1.0
BMI, median (range), kg/m^2	24 (16-32)	24 (19-29)	26 (18-38)	0.70
Distance from the AV, median (range, cm)	8 (2-15)	10 (5-14)	7 (3-10)	0.43
ASA score, n (%)				0.98
1	5 (25)	4 (20)	6 (15)	
2	12 (60)	13 (65)	28 (70)	
3	3 (15)	3 (15)	6 (15)	
Neoadjuvant CRT, n (%)	7 (35)	4 (20)	13 (33)	0.28
Clinical TNM staging, n (%)[a]				〈 0.01
Stage I and II	9 (45)	4 (20)	28 (70)	
Stage III	11 (55	16 (80	12 (30)	
Previous abdominal surgery, n (%)	3 (15)	7 (35)	11 (28)	0.21

ASA = American Society of Anesthesiologists; AV = anal verge; CLS = conventional laparoscopic surgery; CRT = chemo-radiotherapy; SPLS = single-port laparoscopic rectal surgery; taTME = transanal total mesorectal excision; TNM = tumour, node, metastasis.
a) American Joint Committee on Cancer, 6th ed.

TABLE 2

Procedural details and perioperative data.

	SPLS (n = 20)	CLS (n = 20)	taTME (n = 40)	p-value
Procedure, n				0.001
LAR	6	1	2	
LAR-I	4	13	33	
Hartmann	2	4	3	
APR	8	2	2	
Length of abdominal incision, median (range), mm	40 (25-125)	133 (70-195)	0	0.001
EBL, median (range), ml	33 (0-300)	100 (0-650)	100 (0-3200)	0.14
Duration of procedure, median (range), min.	295 (108-465)	264 (125-421)	349 (218-525)	〈 0.001
Conversion, n (%)	2	1	1 (3)	1.0
Patients with post-operative complications, n (%)[a]	7 (35)	8 (40)	10 (25)	0.47
Re-operation, n (%)	2	2	6 (15)	1.0
LOS, median (range), days	7 (3-51)	8 (4-30)	8 (5-31)	0.69
Re-admission, n (%)	4 (20)	1 (5)	11 (28)	0.15

APR = abdominoperineal resection; CLS = conventional laparoscopic surgery; EBL = estimated blood loss; LAR = low anterior resection; LAR-I = low anterior resection with protective ileostomy; LOS = length of hospital stay; SPLS = single-port laparoscopic rectal surgery; taTME = transanal total mesorectal excision.
a) ≥ 1 complications.

Statistics

The study population was set on an empiric basis as a pilot study because of a lack of previous studies that would allow for a power calculation. Continuous data are presented as median (range) and were non-normally distributed. Within-group comparison was made using the Friedman test for repeated measures, and the Kruskal Wallis test was applied for between-group comparison for each time point. Categorical variables were compared using the chi-squared test. p-values < 0.05 were considered statistically significant. Graphical presentations were made by GraphPad Prism version 6. Statistical calculations were made using SPSS version 24 (SPSS Inc., Chicago, IL, USA).

Ethics

The protocol for single-port project was previously registered with ClinicalTrial.gov, and it was conducted in accordance with the principles of the Declaration of Helsinki; the protocol was approved by the local ethics committee. The taTME trial was also conducted in accordance with the principles of the Declaration of Helsinki, and the protocol was approved by the local ethics committee.

Trial registration: ID NCT 0157972, ethical approval ID H-1-2011-007, H-15000540.

RESULTS

Twenty patients with CLS and 20 patients with SPLS from a historic cohort and 40 patients with taTME were included in the study. Patient characteristics are presented in **Table 1**. We observed differences in tumour characteristics (less clinical stage III in the taTME group).

Table 2 summarises the procedural details and perioperative data for the three groups. The majority of the patients in the taTME group were treated with low anterior resection and loop ileostomy. Patients in the CLS group had a longer median length of abdominal incision than patients in the SPLS group (133 mm versus 40 mm, $p < 0.001$).

There were two conversions in the SPLS group due to insertion of an additional laparoscopic 10-mm port

to facilitate stapling in one patient and to facilitate mobilisation of a tumour in the pelvis in another patient. There was one conversion to open surgery due to a large tumour in the CLS group. The estimated blood loss was comparable in all groups (p = 0.14). However, one patient in the taTME group had a blood loss of 3,200 ml. The patient had severe intra-abdominal obesity and the tumour was fixed to the lateral pelvic wall. Internal iliac vein bleeding occurred during the pelvic dissection and the case was converted to open surgery with a large Pfannenstiel incision. Hereafter, a Hartmann's procedure was performed, and the post-operative course was uneventful.

Three patients in taTME group underwent Hartmann's procedure. One was converted to open surgery as mentioned above, and the rectum distal of the tumour was transected with Contour stapler. One of the two other patients was an 82-year-old man with partial incontinence. The tumour was located 6 cm from the anal verge. The stump was closed with purse-string suture. He had a urinary retention as a post-operative complication, and the post-operative period was otherwise uneventful. The other patient was a 66-year-old man with a stenotic rectal tumour infiltrating the surrounding tissues, approximately 10 cm from the anal verge. There were also a few small abscesses. We preferred not to do an anastomosis and closed the rectal stump with purse-string suture. Both patients underwent R0 resection.

The median operative time was significantly longer in the taTME group ($p < 0.001$). The rate of post-operative complications was comparable between the three groups (**Table 3**). However, post-operative urinary retention and re-admissions occurred more frequently in the taTME group. Two patients died in the SPLS group: an 86-year-old American Society of Anesthesiologists III patient died on the 39th post-operative day due to severe pulmonary oedema, and an 83-year-old female patient with an uneventful post-operative course was found dead at home one week after her hospital discharge. There was no mortality in the taTME and CLS group.

Pathological analyses of the resected specimen are summarised in **Table 4**. There was a difference in the macroscopic quality of the TME specimen (mesorectal fascia (MRF)) between the three groups, with more patients in the taTME group having an incomplete MRF ($p < 0.01$). Furthermore, a difference between the groups was seen regarding the distant resection margin ($p < 0.01$).

In each group, plasma levels of CRP and WBC changed significantly before and after surgery ($p < 0.001$). However, there was no difference in the levels of CRP and WBC between the three groups ($p > 0.05$) (**Figure 1**A and B).

DISCUSSION

This cohort study was conducted to investigate the inflammatory response following three minimally invasive approaches in rectal cancer surgery. We failed to demonstrate a difference in the immune response between SPLS, CLS and taTME. Some studies with minimally invasive procedures such as laparoscopic cholecystectomy have shown a decrease in the level of acute-phase reactants.

TABLE 3

Post-operative complications.

	SPLS (n = 20)	CLS (n = 20)	taTME (n = 40)	p-value
Patients with ≥ 1 complications, n	7	8	10	0.46
Complications, n				
Superficial perineal wound infection/dehiscence	2	0	0	-
Urinary tract infection	2	1	3	0.85
Urinary retention	1	0	7	0.07
Prolonged post-operative ileus	0	1	1	-
Cerebral vascular accident	1	0	1	-
Pelvic abscess	0	1	2	-
Anastomotic leakage	4	4	4	-
Rectovesical fistula	0	1	0	-
Ischaemic colon	0	0	2	-
Sepsis	0	0	1	0.60
Intra-abdominal bleeding	0	0	1	-
Epididymitis	0	0	1	-
Total	10	8	23	0.44

CLS = conventional laparoscopic surgery; SPLS = single-port laparoscopic rectal surgery; taTME = transanal total mesorectal excision.

TABLE 4

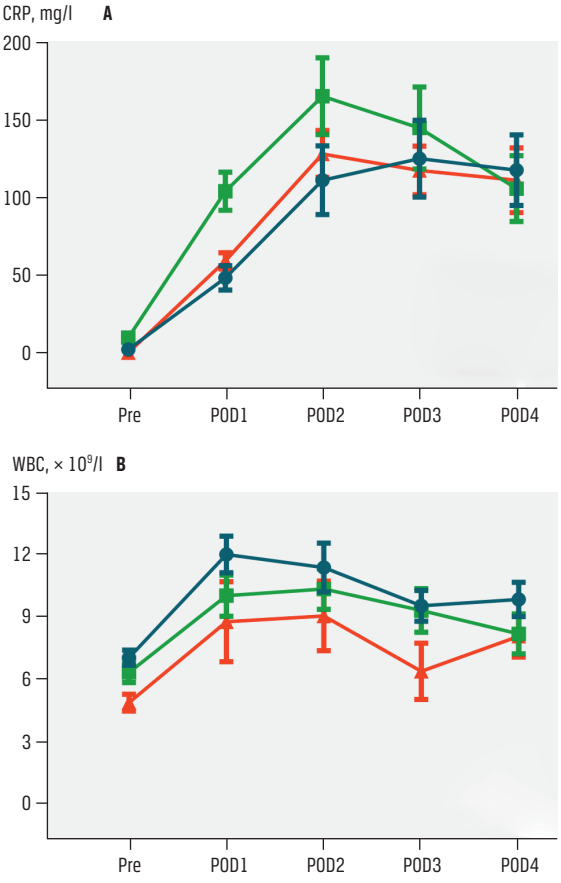
Pathological details and follow-up.

	SPLS (n = 20)	CLS (n = 20)	taTME (n = 40)	p-value
Harvested lymph nodes, median (range), n	14 (4-33)	19 (7-33)	22 (8-96)	0.01
Length of specimen, median (range), cm	21 (11-35)	20 (14-25)	20 (9-43)	0.87
Tumour size, median (range), mm	25 (10-70)	40 (20-75)	33 (3-103)	0.06
MRF, n				< 0.01
C or NC	20	19	29	
IC	0	1	11	
CRM, median (range), mm	10 (0-43)	7 (1-25)	7 (0-32)	0.43
DRM, median (range), mm	32.5 (5-75)	25 (10-65)	15 (2-60)	< 0.01
Complete resection, n	19	20	39	1.0
Clinical TNM staging, n (%)[a]				0.25
Stage I and II	17 (85)	15 (75)	26 (65)	
Stage III	3 (15)	5 (25)	14 (35)	
Follow-up, median (range), mo.s	12 (6-18)	15 (6-20)	29 (1-30)	0.30

C = complete; CLS = conventional laparoscopic surgery; CRM = circumferential resection margin; DRM = distal resection margin; IC = incomplete; MRF = mesorectal fascia; NC = nearly complete; SPLS = single-port laparoscopic rectal surgery; taTME = transanal total mesorectal excision; TNM = tumour, node, metastasis.
a) American Joint Committee on Cancer, 6th ed.

FIGURE 1

Blood levels of C-reactive protein (CRP) (**A**) and white blood cell count (WBC) (**B**) for transanal total mesorectal excision (-●-), single port laparoscopic surgery (-■-), and conventional laparoscopic surgery (-▲-). Blood samples collected before surgery (Pre), post-operative day (POD) 1, 2, and 3. No difference was seen between the three groups.



The reduction of parietal trauma in laparoscopic surgery is thought to be one of the aetiological factors for this improvement. However, no robust evidence has been published supporting a better-preserved host immune function following laparoscopic colorectal surgery, although we observed a trend towards improvement. Veenhof et al investigated stress response after laparoscopic and open rectal surgery and found that short-term post-operative immune and inflammatory functions tended to improve with the laparoscopic approach. But the differences were not consistent at all time intervals, making it difficult to draw a definitive conclusion [11].

We hypothesised that the lack of abdominal incision and thereby reduced surgical stress would further decrease the immune response. The transition from open surgery to laparoscopic surgery has decreased the surgical stress response significantly, but it seems as if the surgical stress response has reached a lower plateau when it comes to the length of incision, possibly reflecting a similar intraabdominal trauma regardless of the type of minimally invasive procedure when comparing CLS with abdominal incision, SPLS incision and taTME with anal specimen retraction. The surgical trauma extends beyond the abdominal incision, but also depends of the intraabdominal handling of the tissue. The high rate of incomplete MRF in the taTME group might reflect more traumatisation of tissue during dissection through the transanal access and maybe a relatively increased immune response as a result.

We also observed a longer operative time in the taTME group. Our taTME operations were performed as a one-team approach, which is a more time-consuming procedure due to the preparation of the patient and staff in the operating room. That has been a main factor prolonging the operating time. In addition, there is also an inherent bias regarding the learning curve. High readmission rates in the taTME group were principally due to a high number of LAR with protective ileostomy and some of these patients had stomal problems with a high ileostomy output, electrolyte deficits and intermittent episodes of sub-ileus that warrant re-admission. Two patients with ischaemic colon in the taTME group belong to the period of our initial experience with taTME. Initially we did not routinely perform mobilisation of the splenic flexure. Transanal extraction and the stretching of the mesenterium of the proximal colon could result in avulsion of the marginal artery due to shear stress at a point more proximal than the selected place of colonic division. That may explain the colonic ischaemia. We also observed a trend towards a higher rate of urinary retention in the taTME group. The number of older male patients and the learning curve in taTME group may explain that. Our results seem to be comparable to those of previous reports on taTME [5, 12, 13]. The taTME Registry Collaborative reported the outcome for 720 patients from 23 countries and concluded that taTME appears to be oncologically safe with acceptable short-term patient outcomes, with a post-operative morbidity of 33%, a conversion rate of 6%, R1 resection of 3% and intact TME specimens in 85% of cases [12]. A recent systematic review reported that the average conversion rate was 3% and the complication rate was 40%, of which 12% were major complications [13]. It was furthermore shown that lower conversion rates, higher major post-operative complication rates and lower rates of intact TME specimens were found in low-volume centres ($n \leq 30$) compared with high-volume centres ($n > 30$).

Five studies have evaluated laparoscopic TME versus taTME [14-18] with different results. Two studies found a shorter operating time and increased length of distal resection margin with taTME [19, 20]. Velthuis

et al reported better TME quality with taTME as compared with CLS [17]. However, the remaining two studies found no difference in resection quality and short-term clinical results [15, 18]. In the present study, there was no major difference in clinical outcome between SPLS, CLS and taTME. However, histopathological outcome was not comparable with a significantly more incomplete MRF in the taTME group. The literature regarding quality of life and anorectal function following taTME is limited, but it seems that most functional scores return to preoperative values except for social function and anal pain, which remain poorer [19].

We found that taTME may be considered a reasonable alternative in selected cases. The taTME approach may be a choice for male patients with a narrow pelvis and in patients with high BMI. While it is commonly accepted that taTME is not suitable for tumours with possible sphincter involvement, the optimal tumour localisation in the rectum for taTME is a subject of discussion, and whether taTME is more suitable for low or mid-rectal tumours remains unknown. Despite a rising number of cohort studies reporting outcomes for taTME, a randomised clinical trial is missing. COLOR III, a multicentre randomised clinical trial comparing taTME with laparoscopic TME for low and mid rectal cancer (NCT02736942), is ongoing and estimated completion is by 2020 [20].

This study has some limitations. It is a non-randomised observational cohort study including a limited number of patients and there is a risk of selection bias. Additionally, our material has a poor match between clinical staging and the use of neoadjuvant therapy, which can make interpretation difficult. A longer follow-up and functional outcomes are missing. Furthermore, the assessment of immune response due to surgical trauma should preferably have been extended to include additional blood markers for immune response.

CONCLUSIONS

There is no difference in the inflammatory response in patients with rectal cancer undergoing taTME compared with CLS and SPLS. It is therefore suggested that the length/presence of abdominal incision does not have a major impact on the inflammatory stress response in the post-operative phase. The intra-abdominal handling of the tissue may also play a role. The present study should be considered hypothesis generating for future well-designed randomised multicentre studies.

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