

Incidence and Risk Factors for Anastomotic Failure in 1594 patients treated by

Transanal Total Mesorectal Excision:

Results from the International TaTME registry

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MINI-ABSTRACT

The present international multicenter study reports the incidence and risk factors for anastomotic failure following transanal total mesorectal excision in 1594 reconstructed cases. The anastomotic failure rate is 15.7% with male, obese, diabetic, smokers with large tumours being most at risk.

ABSTRACT

Objective

To determine the incidence of anastomotic-related morbidity following Transanal total mesorectal excision (TaTME) and identify independent risk factors for failure.

Background

Anastomotic leak and its sequelae are dreaded complications following gastrointestinal surgery. TaTME is a recent technique for rectal resection, which includes novel anastomotic techniques.

Methods

Prospective study of consecutive reconstructed TaTME cases recorded over 30 months in 107 surgical centers across 29 countries. Primary endpoint was “anastomotic failure”, defined as a composite endpoint of early or delayed leak, pelvic abscess, anastomotic fistula, chronic sinus or anastomotic stricture. Multivariate regression analysis performed identifying independent risk factors of anastomotic failure and an observed risk score developed.

Results

1594 cases with anastomotic reconstruction were analyzed; 96.6% performed for cancer. Median anastomotic height from anal verge was 3.0 ± 2.0 cm with stapled techniques accounting for 66.0%. The overall anastomotic failure rate was 15.7%. This included early (7.8%) and delayed leak (2.0%), pelvic abscess (4.7%), anastomotic fistula (0.8%), chronic

sinus (0.9%) and anastomotic stricture in 3.6% of cases. Independent risk factors of anastomotic failure were: male gender, obesity, smoking, diabetes mellitus, tumors >25mm, excessive intraoperative blood loss, manual anastomosis and prolonged perineal operative time. A scoring system for pre-operative risk factors was associated with observed rates of anastomotic failure between 6.3% to 50% based on the cumulative score.

Conclusions

Large tumors in obese, diabetic male patients that smoke have the highest risk of anastomotic failure. Acknowledging such risk factors can guide appropriate consent and clinical decision-making that may reduce anastomotic-related morbidity.

INTRODUCTION

Anastomotic leakage (AL) is a common and potentially devastating complication of a colorectal anastomosis and can result in severe morbidity and mortality, as well as long-term anorectal dysfunction.¹ Additionally AL has been reported to increase the risk of local cancer recurrence,² with reduction in overall and disease-free survival.³⁻⁵ AL can markedly impair a patient's quality of life and is detrimental to the doctor-patient relationship,⁶ particularly as AL can result in prolonged sequelae including anastomotic fistulae, chronic sinuses and anastomotic strictures. The reported incidence of AL after colorectal surgery is between 2 and 24%⁷⁻¹⁰ with the highest rates after low anterior resection.^{11,12} The clinical manifestations, and severity, of AL encompasses a broad spectrum of symptoms, and signs, from minor symptoms, to major life-threatening events.

As a consequence of technical developments, particularly stapling instruments, but also minimal access techniques, in combination with widespread adoption of total mesorectal excision as the standard treatment for rectal cancer, the rate of sphincter-preserving surgery with low anastomoses has significantly risen. This reduction in abdomino-perineal excision rates, with an increase in low anastomoses, has led to an increased overall leakage rate in patients with rectal cancer.¹³ Technical drawbacks of minimal access intracorporal anastomosis include the lack of direct tactile sensation, inadequate exposure, and a suboptimal cutting angle of the endo-linear stapler. Crossing staple lines by repeated firings, or incorrect staple height in relation to tissue thickness increase the risk of AL, especially when three or more linear staple firings are needed.¹⁴⁻¹⁵ Transanal total mesorectal excision (TaTME) is the latest advanced surgical access technique for pelvic dissection and facilitates different anastomotic techniques without the need for transabdominal rectal transection, particularly in a narrow pelvis. The standard TaTME technique incorporates an open rectal stump with continuity restored by a coloanal handsewn or double pursestring stapled anastomosis.¹⁶ As

TaTME adoption increases, careful monitoring and review of outcomes is crucial. ~~—With a novel anastomotic technique, I~~ identification of risk factors for AL and overall anastomotic failure may guide preoperative optimization, ~~and the~~ intra-operative surgical decision-making, ~~with adoption of~~ measures to reduce risk and consequences of AL, such as selective defunctioning stomas. This is even more important when a novel anastomotic technique is being implemented into clinical practice.

The primary aim of this study was to report “anastomotic failure” rates and incidence of anastomosis-related morbidity in patients following TaTME surgical procedures recorded on the international TaTME registry. The secondary aim was to identify potential risk factors associated with anastomotic failure.

METHODS

Study design

Cases recorded on the international TaTME registry¹⁷ between July 2014 and December 2016 by 107 surgical centers in 29 different countries (Appendix 1) were analyzed. The registry is a secure online database open to all international surgeons performing TaTME, as previously described.¹⁸ All contributing surgeons were invited via email to update their records with two subsequent reminders to obtain up-to-date data and minimize missing fields. Contributing surgeons were contacted individually to clarify any unexpected or ambiguous data. The primary endpoint of the study was “anastomotic failure” rate, defined as the overall incidence of anastomotic-related morbidity, including early and late AL, pelvic abscess, anastomotic-related fistula, chronic sinus and persistent anastomotic stricture following primary rectal resection. ‘Early’ anastomotic leak was defined as a symptomatic leak diagnosed and managed within 30-days of the primary resection. Anastomotic leaks were classified

according to the ‘International Study Group of Rectal Cancer’ definition and severity grading system (Appendix 2).¹⁹

Statistical analysis

All categorical data are presented as number of cases and percentages, whilst continuous data are shown as either mean \pm standard deviation (range) or median with range. Categorical variables were compared by the Pearson Chi² test, and continuous variables by the two-sample t-test or Mann Whitney U test where appropriate. Risk factors were divided into patient, tumour-related factors, and technical intraoperative factors. Continuous variables were dichotomized using the median or the value at which a significant change occurred as a cut-off point. Variables that achieved a p-value of ≤ 0.100 on univariate analysis were selected for the multivariate analysis to identify independent predictors of anastomotic failure and early AL. Median and mean imputation was used to adjust for missing values where appropriate and first order interactions tested in the multivariate model. A p-value <0.05 was considered statistically significant and odds ratios (OR) and their 95% confidence intervals (CI) are reported. The β coefficients (log odds ratios) derived from the multivariate analysis were used as weights in the derivation of the anastomotic failure observed risk score. Multilevel logistic regression model was used to adjust for possible clustering of anastomotic failure within centers. The Statistical Package for Social Sciences (SPSS) of IBM Statistics, version 24, was used for the analysis.

RESULTS

A total of 1836 cases were recorded on the TaTME registry over a 29-month period. The indication for surgery was rectal cancer in 1663 (90.6%) patients and benign pathology in 173 (9.4%). Overall, 1594/1836 (86.8%) cases had an anastomosis and will be the focus of the

results presented in this paper. Of the remaining 242 non-restorative procedures, 236 were planned as such, leaving 6 (0.4%) cases in which the anastomosis was abandoned (Supplementary Table 1).

Patient and tumour characteristics

Table 1 outlines patient and tumour characteristics. The majority of registered cases were male patients with a median (range) age of 65 (19–93) years and median (range) body mass index (BMI) of 26.0 (15.6–44.2) kg/m². In total 275 patients (17.3%) had previous unrelated abdominal surgery, including 21 (1.3%) prior prostatectomy. Twelve patients (0.8%) had received pelvic radiotherapy prior to diagnosis of rectal cancer. The indication for surgery was rectal cancer in 1540 (96.6%) of reconstructed cases with a median tumour height from anorectal junction on staging MRI of 4.0 (0–14) cm. Radiological cancer staging was reported as stage 0, I, II, III and IV in 17 (1.2%), 267 (19.5%), 287 (20.9%), 689 (50.2%) and 112 (8.2%) cases respectively. Pre-operative involvement of the circumferential resection margin (CRM) was seen on 274 (23.4%) staging MRI scans and 895 (56.1) patients received neoadjuvant therapy; the majority as long course chemoradiotherapy.

Intraoperative details

Operative details are summarized in Table 2, showing that the commonest operation performed was a low anterior resection in 89%, with synchronous operating by two teams in 41.7%. The abdominal phase was performed laparoscopically in 1350 (86.3%) with SILS, open surgery and robotic approaches in 179 (11.4%), 26 (1.7%) and 10 (0.6%) respectively. The recorded estimated blood loss was 0-99mls in 42.3% and 100-499mls in 21.1%. In 32 (2.1%) blood loss > 500mls was reported, mainly due to pelvic bleeding and splenic hemorrhage following splenic flexure mobilization. The specimen was extracted transanally

in 43.9%, whilst abdominal extraction was utilized in the remainder either via Pfannenstiel incision (26.6%), iliac fossa/stoma site (14.8%), umbilical opening (6.7%) or the laparotomy incision (8.0%). A pelvic drain was inserted in 1134 patients (71.1%).

The commonest anastomotic technique performed was mechanical stapling in 66% with an end-to-end or side-to-end configuration in 94% of cases (Table 2). The stapler diameters used included 25-28mm, 29mm, 31-32mm and 33mm in 14.5%, 22.3%, 17.4% and 45.8% respectively.

Intraoperative adverse events occurred in 487/1594 (30.6%). Conversion to an alternative technique was required in 90 patients (5.6%). Abdominal access conversion was primarily required due to limited visualization secondary to excessive adhesions and obesity, whilst perineal conversions occurred after difficulty identifying the correct dissection plane leading to bleeding and/or visceral injuries. Twelve cases underwent both perineal to abdominal, and minimal access to open abdominal conversions, and were predominantly men (11/12) with a higher BMI (mean $27.1 \pm 3.9 \text{ kg/m}^2$). Table 2 outlines the incidence of technical transanal difficulties and adverse events. A total of 41 visceral injuries were recorded during both abdominal and transanal phases; 12 (0.8%) urethral injuries, 7 (0.4%) rectal tube perforation, 5 (0.3%) vaginal perforations, 5 (0.3%) ureteric injuries, 5 (0.3%) enterotomies, 3 (0.2%) bladder perforations, 2 (0.1%) hypogastric nerve divisions, 1 (0.06%) splenic injury with significant hemorrhage, and 1 (0.06%) diaphragmatic perforation during splenic flexure mobilization. Anastomosis-related technical difficulties included anastomotic defects requiring additional handsewn sutures (n=12), complete re-do of the anastomosis due to ischemia (2) or rectal tear (1). Further intraoperative complications included injury to the mesenteric vascular arcade during attempted transanal specimen extraction, carbon dioxide embolism with hemodynamic instability and intraoperative myocardial infarction.

Post-operative outcomes and Anastomosis-related morbidity

The median length of hospital stay was 8 days (range 2 to 94), with morbidity and mortality rates within 30-days of the primary resection of 35.4% and 0.6% respectively. Overall, 44 deaths (2.8%) have been reported over a mean follow up period of 14 months (range 3–68). Post-operative complications within 30-days, categorized according to the Clavien-Dindo classification²⁰ as I/II, III, IV and V, occurred in 354 (22.2%), 188 (11.8%), 13 (0.8%) and 9 (0.6%) patients respectively. Emergency surgical re-intervention **for any cause within 30-days or index admission** was required in 128 (8.0%) (Supplementary Table 2: Summary of emergency operations).

Table 3 outlines the incidence of anastomosis-related morbidity, showing an overall anastomotic failure rate of 15.7%. Early AL, diagnosed within 30-days of the primary resection, occurred in 124 (7.8%) patients; 68 (61.3%) of these were managed by active therapeutic intervention without the need for a re-laparotomy (Grade B). Overall 311/1594 patients required **a re-intervention for any cause at some point during the study period, whilst 135/311(43.4%) of these re-interventions were required for anastomotic failure. A total of 141 interventions were reported during the study period.** The majority, 108/141 (76.6%), of re-interventions for anastomotic failure involved surgery under general anesthesia, with either examination of the anastomosis with washout \pm vacuum therapy, re-suturing for anastomotic dehiscence, laparoscopic lavage \pm defunctioning stoma or as a later re-operation with dilatation or anastomotic re-fashioning for anastomotic stricturing. **Out of 250 patients diagnosed with anastomotic failure, 219 had a defunctioning stoma created at the index operation. Gut continuity was restored in 124 (56.6%). The median interval to stoma closure was 142 days (approx. 4½ months), range 5–1638 days. Twelve patients (0.8%) underwent a takedown of the anastomosis with an end stoma in the form of a Hartmann's procedure for**

anastomotic leak (11 cases) and a completion proctectomy with end colostomy for a tight anastomotic stricture (1 case). A further six patients (0.4%) with anastomotic leaks were managed with laparoscopic washout and formation of a defunctioning stoma.

Histopathological results for the 1540 cancer cases are described in supplementary table 3. In summary, a curative R0 resection rate was achieved in 95.7%. A positive CRM or distal resection margin (DRM) was reported in 60 (3.9%) and 10 (0.6%) cases respectively. Major defects in the TME specimen and rectal perforations were noted in 75 (4.9%) specimens.

Risk factors for early anastomotic leak

Univariate analysis identified eight patient-related and five technical risk factors (p value ≤ 0.100) for early AL (Table 4). On multivariate analysis, seven of these factors remained statistically significant. Patient-related risk factors included male gender, obesity, smoking (borderline significance), diabetes, larger tumors ($>25\text{mm}$ maximum diameter), and tumor height $>4\text{ cm}$ from anorectal junction on MRI. The only significant technical risk factor was excessive intraoperative blood loss of $\geq 500\text{mls}$. Significantly more cases that did not have a defunctioning stoma ~~that~~ developed an early symptomatic AL ~~did not have a defunctioning stoma~~ compared to those that were defunctioned (12.4% vs. 7.2%, OR 0.547, 95% CI 0.334–0.895, $P=0.015$). Although univariate results suggested that patients who did not receive neoadjuvant therapy were at higher risk of AL and failure (Tables 4 & 5), these findings were not significant on multivariate analysis and outcomes are confounded by significantly more patients who had neoadjuvant treatment had defunctioning (32.8% vs 58.1%, OR 2.846, 95% CI 2.042–3.967, $P<0.001$). Defunctioning stoma was not included in multivariate analysis as previous studies have shown that the presence of a defunctioning stoma may not prevent AL, but rather reduces the consequences should an AL occur.²¹ Hence, a defunctioning stoma is

proposed as a strategy to reduce the adverse effects of AL and is recommended in patients with identified risk factors .

Risk factors for anastomotic failure

Fourteen potential risk factors associated with anastomotic failure were identified on univariate analysis (Table 5). Eight of these (5 patient-related and 3 technical factors) remained statistically significant on multivariate analysis including male patients, obesity, smoking, diabetes, larger tumors over 25 mm, manual anastomoses, excessive blood loss of ≥ 500 milliliters, and longer perineal phase operative time of >1.5 hours. The manual technique significantly increased the risk of late stricturing (5.9% vs. 2.7%, OR 0.448, 95% CI 0.263–0.762, $p=0.002$). The presence of a defunctioning stoma did not appear to significantly influence the incidence of anastomotic failure in this cohort (no stoma 17.5% vs. stoma 15.6% OR 0.872, 95% CI 0.576–1.320, $p=0.516$). Multilevel regression analysis did not demonstrate any significant clustering between hospitals for anastomotic failure rates, nor alter the significant risk factors. Figure 1 shows the scoring of patient and tumour-related risk factors and the associated percentage risk of developing anastomotic failure observed in this cohort of 1594 patients treated by a TaTME technique with a low anastomosis.

DISCUSSION

Anastomotic complications can lead to significant early complications and long-term morbidity, with a possible adverse impact on cancer outcomes.^{2,22,23} Identifying high-risk patients and implementing appropriate reduction strategies, through pre-operative patient optimization, technical considerations and focused post-operative management with early recognition of adverse signs, are key to improving patient outcomes.

In contrast to abdominal rectal resections, usually with a stapled distal transection, TaTME involves a transanal endoscopic full rectotomy, with an open rectal stump. A number of stapled and handsewn techniques have been reported to perform an anastomosis after TaTME.¹⁶ Most reports are small numbers with little data on the morbidity associated with anastomoses following TaTME.

Results from the recently commenced randomized controlled trials comparing TaTME with laparoscopic TME may provide some robust data in the future, should sufficient numbers be enrolled.^{24,25} Currently, the international TaTME registry¹⁷ provides the largest cohort of TaTME cases performed in the wider surgical community, allowing analysis and monitoring of outcomes, and incorporating outcomes from units with different levels of surgical experience. In this study 1594 TaTME cases with an anastomosis were analyzed, with an early leak rate of 7.8%. This value is higher than the previously published rate of 5.4% in the initial 720 registry cases¹⁸ and could be explained by increased complexity of cases performed transanally, wider adoption of TaTME by surgeons at the start of their learning curve or improved recording and reporting of adverse events on the registry. Over the last year the number of surgical centers joining the registry has almost doubled with approximately 32 cases recorded per month and 35% of centers having performed less than 5 TaTME cases. Nonetheless, the leak rate remains within an acceptable range comparable to previously reported incidences in colorectal surgery.⁷⁻¹⁰ Similarly, the overall morbidity rate of 35.4% is within recognized rates comparable to conventional abdominal TME surgery, especially when we take into account the majority of cases selected for TaTME are the more difficult low rectal cancer cases.

Although higher leak rates have been attributed to low surgical volume,^{26,27} Hyman et al,²⁸ found that even in a group of high-volume surgeons, leak rates still ranged from 1.6–9.9%; despite more surgical experience and high caseload. This variation may be due to the

multifactorial etiology and contributing factors that lead to AL, including both non-modifiable and modifiable patient and tumour-related risk factors. Independent risk factors identified in previous studies include male gender, smoking, obesity, pre-operative radiotherapy, emergency surgery, and tumour-related factors such as distal infraperitoneal tumors, larger tumour size, and advanced tumour stage.^{13,19,29-31} Our study found similar factors to be significant for AL and overall anastomotic failure, in particular male diabetic smokers with large tumors. Sorensen et al³² reported that smoking impairs tissue healing through nicotine-induced vasoconstriction, reduced perfusion, and carbon-monoxide induced cellular hypoxia, leading to reduced tissue oxygen and collagen deposition. Diabetes also impacts wound healing as uncontrolled hyperglycemia leads to vascular damage, resulting in decreased blood flow and cellular accumulation of toxic glucose-derived metabolites.³³

A recent meta-analysis by Qu et al reported four intra-operative factors significantly associated with increased risk of AL, including longer operative time, number of stapler firings >2, intra-operative transfusions/blood loss >100 mL, and anastomotic level of <5 cm from anal verge.³¹ In TaTME, the distal rectal transection does not involve multiple stapler firings and so eliminates this potential risk factor. However, excessive blood loss and longer operative time were also found to be important factors following TaTME. Interestingly, anastomotic height appeared to be associated with AL only on univariate analysis (but not overall anastomotic failure) and a higher rate of AL occurred in anastomoses at a level of >3 cm from anal verge. Similarly, higher tumors located >4 cm from the anorectal junction on MRI were found to pose a greater risk of leakage than lower tumors, and this remained significant on multivariate analysis. Colorectal surgeons are likely to have less experience in performing a transanal pursestring on an open rectal stump at a higher distance from the anal verge prior to stapled anastomosis in their early phase of the learning curve for TaTME. The lower stapled anastomoses can also be reinforced with additional handsewn sutures that

would be difficult to place more proximally, and any leakage through a lower anastomosis is more likely to discharge transanally rather than accumulating intra-abdominally with symptomatic sepsis.

The evidence regarding manual versus stapled techniques is more conflicting with no significant differences in AL rates, stricture and mortality in colorectal anastomoses reported in a Cochrane review and recent meta-analysis.³⁴⁻³⁵ Cong et al.³⁶ did find significantly lower rates of AL and stricture formation following stapled compared with handsewn coloanal anastomoses after intersphincteric resection. Similarly, our results suggest that the odds of developing anastomotic failure, in particular anastomotic stricture, is 30% less likely if a stapled anastomosis is performed; although no association was noted with early AL. Depending on the degree of anastomotic stricturing, multiple interventions may be required including anastomotic dilatation, re-do anastomoses or even conversion to a permanent stoma; all of which contribute to long-term morbidity and increased healthcare costs.

Reassuringly, 82% of TaTME patients diagnosed with an early AL were successfully managed without the need for a laparotomy. Overall 20.7% were managed conservatively and 61.3% underwent active re-intervention without requiring laparotomy. Similar findings were reported by Kim et al³⁷ in patients with AL following minimally invasive (laparoscopic and robotic) anterior resection, with 19.7% undergoing a second open operation, whilst 69% and 11.3% had laparoscopic re-intervention and transanal surgery respectively. The benefits of a less invasive approach, where feasible, compared with a laparotomy for AL after initial laparoscopic surgery were reported in two retrospective cohort studies^{38,39} with shorter intensive care stay, shorter time to first diet and earlier stoma functioning.

Reduction strategies and treatment algorithms for anastomotic failure have been developed and proposed by numerous authors and surgical societies.^{7,21,40,41} The risk factors and the pre-operative observed risk scoring reported in this study can aid the perioperative planning for

patients undergoing TaTME. The observed risk score does however require validation which is planned using the subsequent future cohort recorded on the registry. Pre-operative optimization with tighter glycemic control for diabetics, weight loss for the obese and active smoking cessation programs can be initiated immediately, especially if more time is available during neoadjuvant treatment or prior to non-urgent benign resections. Operative strategies, such as the formation of a defunctioning stoma, pelvic drain placement, and use of fluorescence angiography,⁴² if available to assess bowel perfusion, should be considered intra-operatively especially if the risk score proposed here is high. Although accurate prediction of risk is impossible, appreciation of these factors may help with the discussion and decision-making with the patient as to whether an anastomosis should even be attempted, especially in the context of poor pre-existing bowel function and/or poor physiological reserve to cope with anastomotic failure.

The limitations of this study include the potential for reporting bias and human error in recording registry data. Post-operative complications, in particular, may be difficult to capture, especially if patients attend a different hospital or are treated in the community. Thus, longer term outcomes are likely to be under-reported. Differences in the investigative methods to diagnose anastomosis-related pathology may further under-report the true incidence or increase heterogeneity amongst groups. Early leaks were also more likely to have been identified clinically and, we therefore cannot address the question of occult or subclinical leaks. However, the main intention was to determine the incidence of symptomatic leaks and to identify potential risk factors. Although the TaTME registry captures over 200 variables, certain factors that may influence anastomotic healing, such as perioperative fluid management and use of vasopressors, are not recorded. Nonetheless, at present, this registry is the largest TaTME database available and encompasses the wider

surgical community performing the technique worldwide with an open and transparent collaborative.

In conclusion, anastomosis-related complications cause significant morbidity and are an ongoing challenge. New and modified anastomotic techniques have been developed to address the open stump following TaTME.¹⁶ Analysis of the risk factors identified in this study for AL and longer-term anastomotic failure aids perioperative management and decision making tailored to the patient to reduce and mitigate complications. Further research is required to determine the learning curve associated with TaTME and the optimal training pathway⁴³⁻⁴⁵ to further reduce the occurrence of adverse events and to optimize the benefits of this novel access technique.

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LEGENDS

Table 1. Patient and tumour characteristics

Table 2. Operative details

Table 3. Anastomosis-related morbidity

Table 4. Univariate and multivariate analyses of patient-related and technical risk factors for early anastomotic leak.

Table 5. Univariate and multivariate analyses of patient-related and technical risk factors for overall anastomotic failure.

Figure 1. Anastomotic Failure Observed Risk Score

Supplementary table 1. Non-restorative procedures

Supplementary table 2. Post-operative morbidity: Emergency surgery re-interventions

Supplementary table 3. Histopathological data for cancer cases

Appendix 1. Contributing surgical centers and collaborators to the TaTME registry cases reported

Appendix 2. Definitions and references of variable parameters used

