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Title Page

Investigations and time trends in loop ileostomy reversals following anterior resections: a single Australian institution seven-years' experience

Running head: Investigations in ileostomy reversal

Key words: ileostomy reversal, contrast enema, sigmoidoscopy, time trends

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Abstract

Background: Currently no consensus exists regarding what pre-reversal investigations are required to assess integrity of the rectal anastomosis. The objective of this study was to compare pre-reversal assessments of anastomotic integrity and to evaluate trends that might have influenced timings for reversal.

Methods: From a prospectively maintained database, patients with colorectal cancer resections between March 2012 to October 2019 were identified. Patient characteristics, pre-reversal contrast enema and flexible sigmoidoscopy findings were recorded, and management of complications were recorded. Time-to-ileostomy reversal and time series for trends were analyzed.

Results: There were 154 patients included. Pre-reversal contrast enema or sigmoidoscopy detected a possible stricture or leak at the rectal anastomotic site in 11% (15 of 132) and 15% (18 of 112) respectively. When both modalities were used there was concordance of 86.1% and a positive likelihood ratio of 5.73. Of 125 (81.2%) ileostomies reversed, the median time-to-reversal was 11.99 months; time series analysis over the 7-year period showed no significant trend for average patient-days from booking to reversal (P = 0.60). Cox regression modelling did not identify any influential risk factors for the times taken to reversal.

Conclusion: This study supports the use of both contrast enema and flexible sigmoidoscopy in the assessment of rectal anastomosis integrity. Most patients with complications can have their ileostomies reversed. Patients who have adjuvant chemotherapy have a prolonged time to reversal.

Introduction

Temporary diverting loop ileostomies are commonly constructed to mitigate the clinical consequences in the event of rectal anastomotic leaks following anterior resections. The Australian Institute of Health and Welfare recorded 4442 anterior resections of the rectum between the years 2016-17[1]. The clinical and economic burden of temporary ileostomy for rectal cancer have been addressed in relation to adverse influence on total hospital stay and aspects of Health-Related Quality of Life (HRQOL)[2]. Prompt ileostomy reversal should be a priority when feasible.

Reversal of a diverting loop ileostomy in the presence of a leak or stricture at the rectal anastomotic site is associated with poor surgical outcomes[3]. No clear guidelines exist as to what investigations are essential in order to accurately assess the rectal anastomosis prior to reversal. In the published literature, both water-soluble contrast enema (WSCE) and flexible sigmoidoscopy (FS) have been advocated[3-7].

Timing of reversal can vary significantly depending on numerous factors. Although there are institutions who offer “early” reversal, most institutions offer reversal after patients have completely recovered from their cancer treatment. However, several steps still exist prior to their reversal being carried out. Analysis of time trends for reversal (as distinct from time-to-reversal) over a defined period of sufficient length permit identification of trends and therefore clinical resources can be shifted to accommodate the trend[8].

The objectives of this study were to compare pre-reversal methods of anastomosis assessment, to identify the management of complications and to evaluate time series for trends that might have influenced timings for reversal.

Methods

Ethical approval for this project was obtained at Western Health (QA2019.39). This project was a retrospective cohort study using data from a prospectively maintained database supplemented with data from clinical records. All ileostomies constructed in the setting of colorectal cancer resection between March 2012 and October 2019 at Western Health in Melbourne, Australia were studied. Patient follow up was until March 2020. Inclusion criteria was any patient 18 years and older who had a diverting loop ileostomy as a part of the surgical treatment of colorectal cancer. Patients who had ileostomy reversal at another health service were excluded.

Demographic data included age, gender, country of birth, primary language, American Society of Anaesthesiologists (ASA) classification score, Body Mass Index (BMI), comorbidities, type of primary resection, mortality, smoking status, key dates (including date of cancer resection, ileostomy reversal work-up), ileostomy pre-reversal investigations, adjuvant chemotherapy, and length of stay (LOS) during ileostomy reversal. The time to reversal was divided into 4 phases. *"Not ready"* was the time from index resection to booking of first investigation. *"Investigation"* was the time from the first request of either a FS or WCSE to the time of completing the last investigation. *"Management and decision to reverse*" was the time taken to treat any complications related to the anastomosis/time between last test and booking of reversal. *"Wait-listed"* was the time from booking of reversal to reversal operation. Non-reversal was defined as the presence of the ileostomy at the end of follow up. Results from both the water-soluble contrast enema (WSCE) and flexible sigmoidoscopy (FS) were recorded. A true anastomotic stricture was defined as a narrowing seen on FS and a true anastomotic leak was defined as a defect confirmed on both WSCE and FS or if a patient presented with a clinical anastomotic leak.

Statistical analysis

Descriptive data were presented as median and interquartile range (IQR). Likelihood ratio was calculated to assess diagnostic accuracy of the investigations for anastomotic integrity. Kaplan-Meier

estimate was used to analyze time-to-ileostomy-reversals. Log-rank tests for equality of reversal function was applied to select univariate potential confounders (p-value<0.2- 0.25) for Cox proportional hazard regression modelling. Proportional hazards assumption was checked by Schoenfield residuals. Time series data was constructed to detect a trend for average patient-days from booking to reversal. The null hypothesis of no trend was tested with the Mann-Kendall trend test. All statistical tests were two-sided, and the 5% α-level was used to assess significance. Analyses were performed with Stata (v14.2) Stata Corp, College Station, USA and XLSTAT (2018) Addinsoft, France.

Results

Patient characteristics

A total of 154 patients were analyzed. Patient demographics are presented in Table 1. There were 114 male (74%) and 40 female (26%) patients with a median age of 65 years (IQR 58.0-71.0). Ultra-low anterior resections (116, 75%) accounted for most of the primary procedures.

Pre-reversal investigations

For patients that had both investigations, the majority (57/101, 56.4%) were requested on the same day, a further 24 had a FS booked first and the remaining 21 had the WSCE arranged as a first test. However, despite this, most patients had their contrast enema done first (n=72/101, 71.3%). Not all patients who have been booked for FS or WSCE had them done by the completion of data collection.

Flexible sigmoidoscopy was performed in 112 (72.7%) patients. Four (3.6%) had a possible anastomotic defect which 3 were confirmed as a leak on contrast enema. In 14 (12.5%) a true stricture was demonstrated with 5 of these were also seen on WSCE, but 7 had a normal WSCE. Two patients did not have a WSCE.

Of the 14 strictures, 9 were passable and 5 were unpassable by the endoscope. Of the 9 passable, 6 were treated with finger dilatation and 3 required no intervention. The management of the 5 unpassable strictures included 1 radiological dilatation, 1 proceeded to a reversal without further intervention, 1 did not proceed to reversal as deemed "unsafe" following a MDT discussion, 1 had their redo anastomosis delayed due to metastatic disease and one is awaiting endoscopic dilatation.

WSCE were performed in 132 (85.7%) patients. Evidence of a possible stricture occurred in ten (7.6%) and confirmed on FS in 5. Four of these strictures were unpassable and 1 was passable on FS. There was evidence of possible contrast extravasation in five (3.8%) of which 3 were confirmed true leaks.

Of the 101 (66%) patients who had both WSCE and FS, there was concordance of 86.1% and a positive likelihood ratio of 5.73; 95% confidence interval (CI) 2.32 to 13.38 and a negative likelihood ratio of 0.58; 95% CI 0.33 to 0.83 (Table 2).

A true anastomotic leak was confirmed on both investigations for 3 patients, and a true stricture on FS for 14 patients.

Eleven (7.1%) patients did not have either investigation performed; 5 did not proceed to reversal of ileostomy (2 died, 2 had significant metastatic disease or comorbidities and 1 was patient choice), 3 proceeded to have their ileostomies reversed (no documentation for reason of test absence) and the final 3 were still awaiting completion of their investigations. One of the patients who had a reversal of ileostomy without the pre-reversal work up, re-presented post-reversal with an anastomotic leak.

Ileostomy reversal

There were 125 (81.2%) ileostomy reversals within the study period (Fig.1). The median time to reversal was 11.99 months (IQR 8.2-14.7). Six patients (4.8%) waited longer than 24 months for their reversal and 29 (18.8%) ileostomies were not reversed at the end of the study. Reasons for non-reversal included

death (n=4), metastatic colorectal disease (n=2), frailty or comorbidities (n=4), patient preference (n=4), persistent anastomotic issues (n=3) and 11 patients are awaiting pre-reversal investigations or a booking date for reversal. It was not clear from the clinical records why 1 patient did not have a reversal. The median LOS for reversal of ileostomy was 4.2 (IQR 3.2-8.0) days and 15 patients required re-admission within 30 days of their ileostomy reversal procedure.

In a sub-group of patients who received postoperative chemotherapy (n=29) the time to ileostomy reversal was much longer compared to those (n=49) who did not (383 vs 203 days); 95% CI for median difference -2.80 to -0.02 months; P= 0.04 (Table 3).

Time series analysis over the seven-year period

Figure 2 shows time series analysis of bi-monthly average patient-days from booking to reversal; no significant trend for this series over the 7-year period was detected (Kendall's tau (τ) 0.08; Sen's slope 0.74; P = 0.60).

Potential risk factors for time-to-reversal

On univariate analysis, Age, ASA and Primary resection type (high AR, low AR, ultra-low AR) were risk factors (P<0.20 to 0.25) for time-to-reversal of ileostomies. Further Cox regression modelling (proportional hazards assumption met) found no significant influential risk factors. Patients who received adjuvant chemotheray had a longer "Not ready" phase; 187.5 days (IQR130.5-236.8) vs 108 days (IQR71-157), but the other time periods were comparable (Table 3).

Morbidity and mortality

Leak of the rectal anastomosis following the index resection and ileostomy formation occurred in only 9 (5.8%) patients. Six were diagnosed clinically whereas three were not identified until the pre-reversal investigations. Seven (77.8%) of these patients went on to have a successful reversal of ileostomy at a

median time of 8.84 months (IQR 6.47-11.48). Only 1 of 125 (0.8%) patients had a leak following their reversal of ileostomy and it was diagnosed clinically. All-cause mortality at the end of the study was 12.3% (19/154), with only 3 (1.9%) within 1 year, and 1 (0.6%) within 30 days of cancer resection. There was no mortality attributed to the ileostomy reversal, however 1 patient died within a month of reversal and another within a year.

Discussion

The routine use of investigations prior to ileostomy reversal have been questioned and the accuracy of these tests can be variable[3-7]. For example, a "dog ear" at the stapled anastomosis may be misinterpreted as a leak, or a stricture being incorrectly described due to a lack of anastomotic distension on WSCE[4]. Flexible sigmoidoscopy is useful in confirming the presence and degree of a stricture but may not be able to accurately differentiate a leak from a small diverticulum.

However, most centres will perform pre-reversal investigations, with a preference of a contrast enema[3-7]. Our study has shown the importance of performing both WSCE and FS. For example, 7 strictures identified on FS were not seen on WSCE, and of 4 possible leaks on FS, 3 required confirmation on WSCE. Our experience is that FS are better at identifying the presence of strictures and in many cases, we are able to offer prompt intervention. Contrast enema is a more readily accessible investigation but requires radiologists with experience to understand underlying surgical anatomy. The diagnostic performance when both modalities were used had a concordance of 86.1%, and a positive likelihood ratio of 5.73, implying six times more likelihood of correctly detecting leaks/strictures among patients[9].

In this study (Fig.1) the time from index operation to the reversal of the ileostomy (median 11.99 months; IQR: 8.2-14.7) was longer compared to published studies[10-13]. To better understand waiting times to reversal, we therefore divided the reversal pathway into 4: "Not ready", "Investigation", "Management and decision to reverse" and "Wait-listed". The initial "Not ready" period was largely

dependent on the clinical evaluation of patients' suitability for reversal. Patients having adjuvant chemotherapy was found to have an ileostomy for a significantly longer period of time, and this was due to the time required in the "Not ready" period. Apart from this, no other risk factors affected time-to-reversal. Within the literature, socioeconomic factors can be associated with stoma reversal rate[14]. Our cohort of patients came from a diverse cultural background and these factors did not seem to affect time-to-reversal. As time intervals are not independent for the number of reversals performed, we used time series modelling for our analysis[8]. We found over our study period, there was no significant trend (P= 0.60) for the series (Figure 2).

The incidence of anastomotic leak following the index operation in this cohort was 9 (5.8%) which is low[4,15]. The median LOS after ileostomy reversal was 4.2 days (IQR 3.2-8.0) and again was lower than reported[16,17]. The 15 patients that required re-admissions within 30 days of ileostomy reversal were of mixed presentations of "ileus", colitis/enteritis (only 1 confirmed *Clostridium Difficile* colitis which responded completely with antibiotics) and peri-stoma skin inflammation; none required surgical interventions.

Strengths and limitations

The strength of this study included the comparison of test results prior to ileostomy reversal as well as the robust analysis of patient flow; particularly the breaking down of steps involved. The limitations of this study relate to potential inaccuracies related to retrospective collection and interpretation of data from medical records.

Conclusion

This study supports the combined use of both contrast enema and flexible sigmoidoscopy as part of the work up in the reversal of ileostomies. Most patients with complications can have their ileostomies reversed. Patients who have adjuvant chemotherapy have a prolonged time to reversal.

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Conflicts of interest

None declared.

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Figure legends:

Fig. 1. Kaplan-Meier estimate: Time to loop ileostomy reversal (n=125) after anterior resection.

(↓) median time to reversal 11.99 months (95% CI 11.04 to 13.34). Censored n=29 (not reversed).

25% of ileostomies were reversed by 8 months; 75% of ileostomies were reversed by 17 months.

Fig. 2. Time series plot of bi-monthly average patient-days from booking to reversal. Mann-Kendall trend test (two-tailed): Kendall's tau(τ) 0.08; P= 0.60; —●— Sen's slope: 0.74. No significant trend detected.

Table 1: Demographics and baseline characteristics

Category	n (%)
Sex	
Female	40 (26)
Male	114 (74)
Age (median, IQR) †	65 (58-71)
Born in Australia	59 (38.3)
English as first language	95 (61.7)
Co-morbidities	
Diabetes	39 (25.2)
Ischaemic heart disease	12 (7.7)
Any Respiratory disease	32 (20.6)
Renal disease	15 (9.7)
Other history of malignancy	8 (5.2)
American Society of Anaesthesiologists score	
ASA 1	11 (7.1)
ASA 2	79 (51.3)
ASA 3	64 (41.6)
Mortality	
Deaths	19 (12.3)
30-day mortality	1 (0.6)
Smoking status	
Never smoked	65 (41.9)
Ex-smoker	57 (36.8)
Current smoker	34 (21.9)
Operation type	
High AR ¶	4 (2.6)
Low AR ¶	33 (21.4
Ultra-low AR ¶	116 (75.3)
Restorative Proctocolectomy (IPAA)	1 (0.6)
Laparoscopic Assisted	124 (80.0)
Laparoscopic converted to open	24 (15.5)
Open	7 (4)

† IQR inter-quartile range; ¶ AR: anterior resection

Table 2: Diagnostic accuracy of pre-reversal investigations for leaks and strictures for patients that underwent both Contrast enema (WCSE) and Flexible sigmoidoscopy (FS) ¥

Contrast enema (WCSE)	**Flexible sigmoidoscopy (FS)**	Normal	Leak	Stricture
Normal		79 $^{\alpha}$	1 $^{\beta}$	7 $^{\alpha, \gamma}$
Leak		2 $^{\beta}$	3 $^{\alpha}$	0
Stricture		4 $^{\beta}$	0	5 $^{\alpha}$

¥ numbers are frequencies

α: True Positives. Leak seen on FS and WSCE or stricture seen on FS

β: False positives. Leak seen on only one investigation or stricture on WSCE with a normal FS

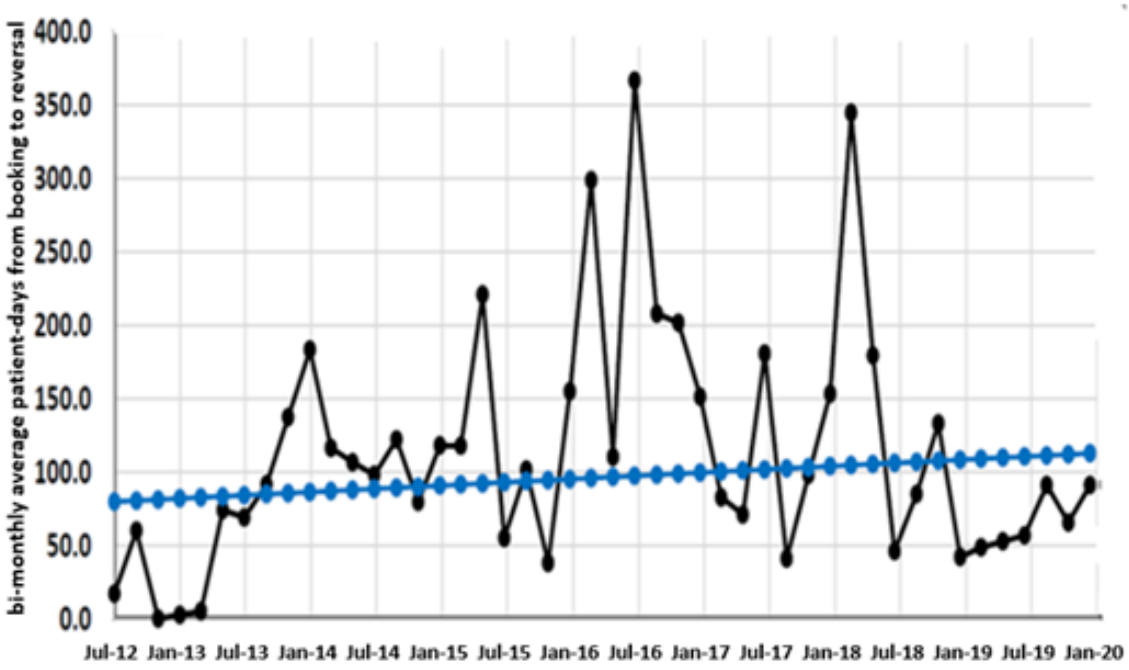
γ: False negatives. Stricture missed on WSCE but seen on FS.

Positive likelihood ratio 5.73; 95% CI: 2.32 to 13.38

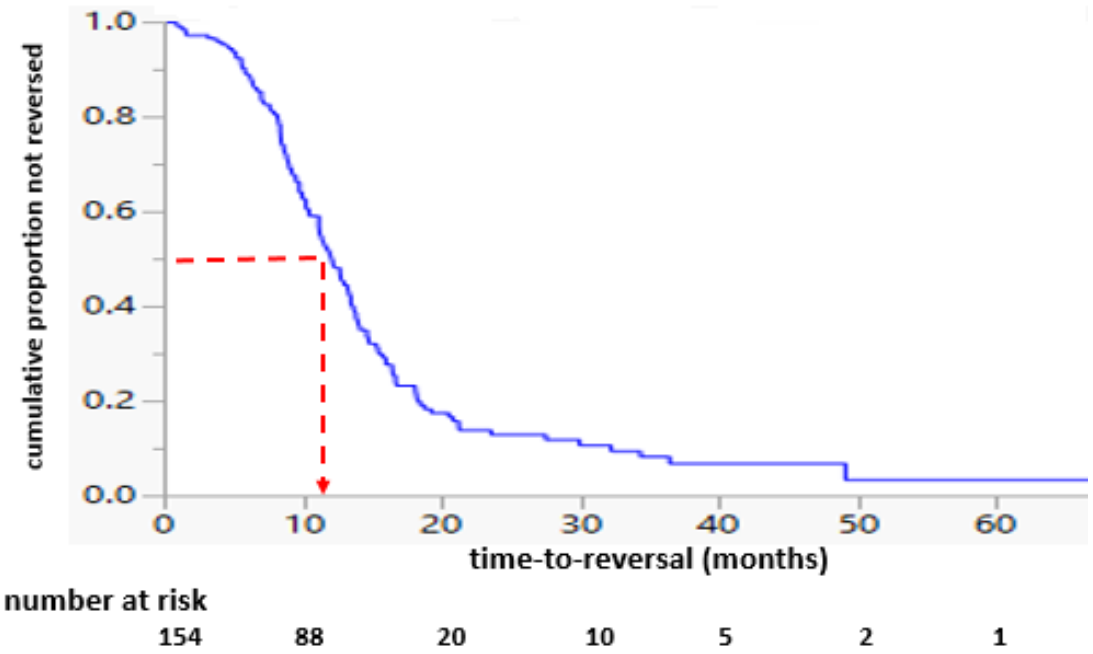
Table 3: Breakdown of 4 key phases in the time from Index resection operation to ileostomy reversal surgery ¥

	#1 Not ready			**#2 Investigations**	**#3 Management and decision to reverse**	**#4 Waitlisted**		**Total time**
Time period	Primary resection to booking test	Booking to first test	First to last test completed	Booking to completing last test	Last test completed to booking reversal surgery	Booking reversal to reversal surgery completed	Primary resection to booking of reversal surgery	Primary resection to reversal surgery completed
All patients (n=125)	135 (89.25- 195.75)	27 (11- 55)	61 (0- 65)	61 (34- 97.5)	16.5 (3.75- 49.25)	77 (40- 154)	233.5 (150.75 - 322)	338 (251- 445)
Received chemotherapy (n=54)	187.5 (130.5- 236.75)	31 (13- 55)	20 (0- 46)	56 (41- 86)	14 (0- 46)	75.5 (40- 168.75)	251 (211- 349)	383(294- 488.5)
No chemotherapy (n=71)	108 (71- 157)	21.5 (8- 55)	21.5 (0- 72.75)	61 (28- 116)	19 (7- 56)	83 (40- 131)	203 (133.5- 302.5)	203 (211- 415.5)

¥ numbers are presented as median days (IQR)



ANS_16483_Fig. 2. Time series plot of bi-monthly average patient-days from booking to reversal. Mann-Kendall trend test (two-tailed).tif



ANS_16483_Figure 1 Kaplan-Meier estimate Time to loop ileostomy reversal after anterior resection..tif