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Protocol for a multicentre, dual prospective and retrospective cohort study investigating timing of ileostomy closure after anterior resection for rectal cancer: The CLOSurE of Ileostomy Timing (CLOSE-IT) study

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ABSTRACT

Introduction A defunctioning ileostomy is often formed during rectal cancer surgery to reduce the potentially fatal sequelae of anastomotic leak. Once the ileostomy is closed and bowel continuity restored, many patients can suffer poor bowel function, that is, low anterior resection syndrome (LARS). It has been suggested that delay to closure can increase incidence of LARS which is known to significantly reduce quality of life. Despite this, within the UK, time to closure of ileostomy is not subject to national targets within the National Health Service and delay to closure exceeds 18 months in one-third of patients. Clinical factors, surgeon and patient preference or service pressures may all impact time to closure, yet to date no study has investigated this. The aim of this UK-wide study is to assess time to ileostomy closure and identify reasons for delays.

Methods and analysis A UK-wide multicentre prospective snapshot study, together with retrospective analysis of ileostomy closure through The Dukes' Club Research Collaborative including patients undergoing ileostomy closure in a 3-month period (April to June 2018) and all patients who underwent anterior resection and ileostomy formation over a historical 12-month period (2015). Time to closure and incidence of 'non-closure' will be calculated. Units will be surveyed to determine local clinical and management protocols and barriers to timely closure. Multivariate linear regression analysis will be used to determine factors significantly associated with delay to ileostomy closure.

Ethics and dissemination Study approved by the South West-Exeter Research Ethics Committee and the Health Research Authority. Study results will be submitted for presentation at international conferences and for publication in peer-reviewed journals. Results will be presented to and discussed with the patient and public representatives and relevant national bodies to facilitate the development of consensus guidelines on optimum treatment pathways.

Strengths and limitations of this study

- The methodology will facilitate rapid patient recruitment from centres across the UK, as the trainee research collaborative structure is now well established and has been used successfully in numerous studies.
- The geographical diversity of The Dukes' Club Research Collaborative will promote study engagement across the UK and ensure that results are widely generalisable.
- The mixed prospective and retrospective arms of the study will together provide data on average UK time to ileostomy closure, incidence of non-closure and will identify factors contributing to delays.
- The study will inform guidelines outlining optimum treatment pathways following ileostomy formation in order to streamline care and reduce delays to closure, with the overall goal to improve patient function and quality of life.

INTRODUCTION

Rectal cancer is common, with over 11 000 cases each year in the UK.[1] The gold-standard surgical treatment for mid to low rectal cancers is sphincter sparing anterior resection. During this, a temporary ileostomy is commonly formed to cover the pelvic anastomosis. Such practice aims to reduce sequelae of anastomotic leak, which includes increased morbidity, mortality and prolonged hospital stay.[2] Unless precluded by patient comorbidity or patient preference, patients will undergo interval closure or reversal of ileostomy, thus restoring bowel continuity. Standard timing for reversal is considered to be 3 months, yet there is limited evidence to inform optimal time of reversal, with recent evidence

suggesting that reversal may be safely performed as early as the first month following initial surgery.[3] In practice, reversal of ileostomy is considered a benign procedure without a cancer driven target in the UK and as such may be delayed due to a variety of factors including patient recovery, postoperative complications or adjuvant chemotherapy, as well as service demand pressures.

As oncological outcomes from cancer surgery have improved, survivor patient-reported outcome measures, including quality of life, have gained increasing relevance. A report commissioned by Department of Health as part of the National Surviving Cancer Initiative demonstrated that 19% of patients with colorectal cancer had difficulty controlling their bowels, confirming previous published reports.[4 5] Unsurprisingly, these symptoms have a profound impact on patients' quality of life, with those patients suffering bowel dysfunction twice as likely to report lower quality of life.[3] Reported symptoms of bowel dysfunction following bowel resection range from stool fragmentation and emptying difficulties, to faecal urgency and incontinence. In the context of rectal cancer surgery, these symptoms are often referred to as low anterior resection syndrome (LARS),[4] with over half of such patients reporting major LARS symptoms.[5]

Crucially, a recent study reported that delay to closure of ileostomy of greater than 6 months was associated with a 3.7-fold increase risk of major bowel dysfunction after restoration of bowel continuity.[5] These data support a previous report which demonstrated a twofold increased risk of bowel dysfunction as measured by the Wexner score[6] and concurrent significant decrease in quality of life in those where ileostomy was closed more than 3 months following index surgery.[7] Despite this, time to closure of ileostomy varies widely across Europe, and is not subject to national targets or financial incentives within the National Health Service (NHS). Outside the UK, closure routinely occurs soon after index surgery, perhaps driven by different funding models, with closure >3 months after initial surgery considered late, as detailed in the recent Scandinavian Early closure of temporary ileostomy (EASY) trial,[8 9] while in the UK, 34% of ileostomies following anterior resection are still not closed at 18 months.[10]

Delay to closure is also associated with patient distress and risk of serious complications while the temporary ileostomy is in situ. A recent large patient consultation exercise undertaken in conjunction with the Association of Coloproctology of Great Britain and Ireland (ACPGBI) found that patients 'put their lives on hold' while waiting for ileostomy closure,[11] while dehydration, renal failure, hospital readmission and local skin complications are also common in such patients.[12 13] The economic cost to delayed closure is clear—complications requiring hospital admission result in significant cost to the health service, yet even routine costs such as stoma appliances and district nursing care incur large cumulative costs across the many thousands of patients waiting for ileostomy closure.

While clinical factors might preclude timely closure, it is possible that surgeon and patient preference, bed shortages or service pressures due to competing national targets, for example, cancer waiting times, might influence time to closure, yet no study to date has evaluated such factors. However, timely closure could be achievable within the modern NHS—an approach that sees ileostomy closure as a continuation of the cancer pathway and a policy whereby patients are given an agreed date for closure on discharge from hospital after their index operation has been demonstrated to result in significant reduction in interval to closure, with 67% ileostomies closed within 12 weeks and 100% patients undergoing ileostomy closure within 12 months.[14] While this approach was of benefit in the author's practice, a full picture of factors impacting interval to closure is required to develop strategies that can be implemented across the UK. A recent pan-European audit undertaken by the European Society of Coloproctology, captured 2527 operations involving reversal of ileostomy/colostomy yet focused primarily on anastomotic technique and will not yield data on timing/delay to closure (The Stoma Closure Audit by European Society of Coloproctology, 2016). There is an urgent need for a multicentre UK study to determine average time to ileostomy closure and factors contributing to delays to closure.

We hypothesise that delay to closure of ileostomy is common in UK surgical practice and that hospital processes increasing waiting times for postoperative outpatient review, relevant investigations and elective surgery, significantly impact time to closure. Our hypothesis continues that units which report low intervals to ileostomy closure will demonstrate streamlined patient pathways to closure which can be incorporated into consensus guidelines for full national implementation.

Context for the research

To date, research in this domain has focused on the impact of delayed closure of temporary ileostomy,[8 10] yet with no consideration of the causes of such delays. The problem (ie, delayed closure) and the potential consequences (bowel dysfunction) are clear, yet the root causes of the problem remain unclear and so solutions cannot be devised. This study is focused on identifying the factors underlying delayed ileostomy closure. These data will fill the current knowledge gap, allow consensus solutions to be produced and best practice guidelines to be devised and implemented.

Aims of the study

The aims of the study are:

- To calculate the time period between formation and closure of ileostomy, following anterior resection for rectal cancer, in the UK.
- To ascertain the causes of delays in closure of ileostomy.
- To develop guidelines outlining optimum treatment pathways following ileostomy formation, thereby streamlining care and reducing delays in closure.

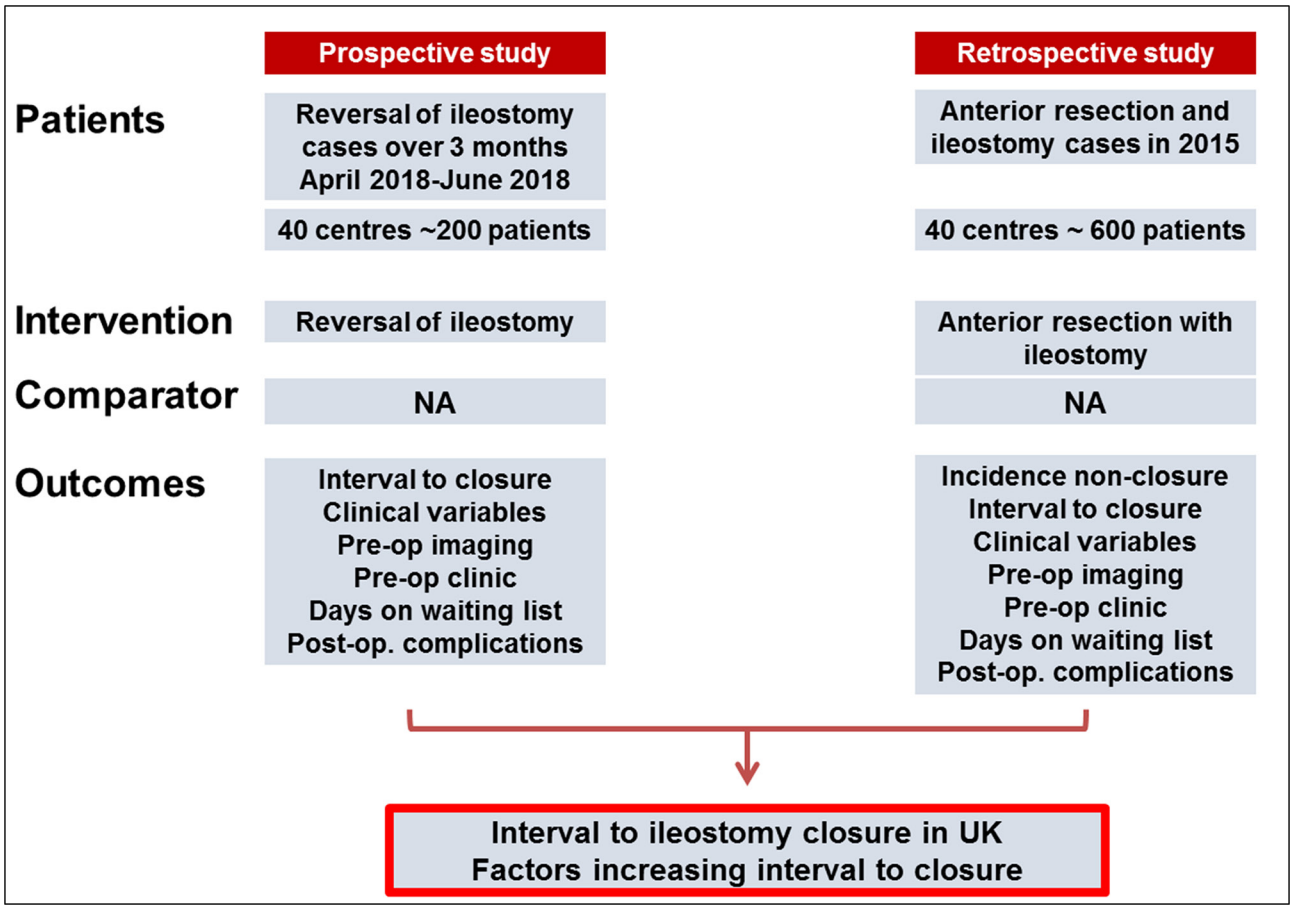

Figure 1 PICO chart for CLOSE-IT study. CLOSE-IT, CLOSurE of Ileostomy Timing; NA, not applicable; PICO, Patient, Intervention, Comparison and Outcome.

Methods and analysis

The study will collect both quantitative and qualitative data relating to ileostomy closure.

Primary outcomes

Duration to closure of ileostomy from index cancer resection surgery

Incidence of non-closure at 18 months.

Secondary outcomes

Factors contributing to delay to closure of temporary ileostomy.

Incidence of complications after ileostomy closure.

Pathways contributing to expedient ileostomy closure.

Study design

There will be two parts to the study; (1) a prospective 3-month data collection of all patients undergoing closure of ileostomy following a previous anterior resection for rectal cancer and (2) a retrospective data collection of patients who underwent anterior resection with ileostomy formation from 2015 to 2016.

Study centres from across the UK have been invited to register the study; to date over 60 centres have expressed interest.

Patient identification and selection

Part 1—Prospective arm: Patients will be identified prospectively from elective waiting lists by local lead investigators. Inclusion criteria: patients 18 years and over at the time of their initial anterior resection; patients who have an ileostomy which was formed during an anterior resection for rectal cancer who are due to undergo ileostomy closure in the 3-month period of data collection (April to June 2018).

Part 2—Retrospective arm: Patients will be identified from prospectively maintained electronic theatre records. Inclusion criteria: patients 18 years and over who underwent anterior resection and ileostomy formation for rectal cancer between 1 January 2015 and 31 December 2015.

Sample size

As there are not comparative outcomes or patient groups within this study, a formal power calculation has not been performed. We have based our patient group sizes on engagement of surgical trainees as investigators in prior national audit studies. Investigators will be sought from across the UK, with our aim to establish data collection from at least 40 centres, with each centre aiming to collect data from 5 prospective patients and 15 retrospective patients. Identification of patients and collection of

data will be closely monitored leading up to and during the active data collection period (see figure 1).

Part 1: 3–5 patients/centre with approximately 40 centres=200 patients.

Part 2: 15 patients/centre with approximately 40 centres=600 patients.

Study workforce, collaboration and promotion

Surgical trainees from across the UK will be recruited to collect and upload patient data to a bespoke Research Design and Conduct Service (Research Electronic Data Capture, REDCap)[15] electronic case report form. Recruitment of investigators and collaborators will be led through the Dukes' Club (the trainee arm of the ACPGBI in collaboration with the National Research Collaborative (NRC) trainee collaborative network. The Dukes' Club will ensure that all trainees have been educated in the methodology of the study as well as data collection to ensure good homogeneity between investigators; there will be both written material and a Twitter chat prior to the start of the data collection period. Study promotion through email newsletters, Twitter and presentation at the NRC National Meeting will promote study collaboration and patient recruitment, while publicising recruitment milestones and individual centre success will encourage other centres to contribute.

Data fields

Data recorded will include: Use of neo±adjuvant chemotherapy±radiotherapy; method of primary surgery (laparoscopic vs open); tumour level from anal verge (on MRI—preneoadjuvant therapy if applicable); imaging performed prior to ileostomy closure (eg, water soluble contrast enema); presence of anastomotic leak following anterior resection requiring either radiological/endoscopic intervention or reoperation; number of days from primary surgery to (1) waiting list entry and (2) closure; patient outcomes following closure including 90-day complications (Clavien-Dindo classification), unexpected 30-day readmission and return to theatre.

Data analysis plan

A bespoke database has been written to facilitate data management for the current study using the REDCap system. This secure web-based data capture system will be maintained and provided by the Cwm Taf University Health Board and will ensure accurate and simple data management and analysis. Data will be cleaned in REDCap and resulting data queries discussed with relevant centres where necessary. Summary statistics for interval from index surgery to closure will be derived through REDCap. Putative factors associated with time will be investigated. Causes of delay will be stratified as clinical or service, to enable differentiation of units with the good practice who incur delays due to clinical factors, from those units where service barriers, such as lack of theatre availability, have caused delays. In brief, univariate comparative analysis of time to closure will be performed using Mann-Whitney U tests using R software.[16] Multivariate linear regression modelling will be used to assess for significant association between clinical factors and time to closure. By convention, all tests will be two sided and $p<0.05$ will be considered statistically significant.

The current study will also collate valuable qualitative systems data from surveys of participating centres. The survey will request information on local treatment pathways and factors that the respondent believes increase or decrease delay to ileostomy closure. The study steering committee (listed above), will independently review survey responses and apply thematic analysis to identify and define recurring themes or patterns relevant to time to ileostomy closure.

Patient and public involvement

We acknowledge the vital role the public and patients play in setting research priorities and in informing study design, ensuring research is fully focused on patient-led priorities. Patients are clearly calling for more research into temporary ileostomy and anterior resection syndrome—attendees at the ACPGBI patient and public involvement (PPI) consultation commented that having a temporary stoma meant 'putting life on hold',[11] with suggestions that delays in closure obstructs the return to normal activities and psychological recovery. Meanwhile, patient discussion forums provide a clear indication of the distress caused by symptoms following ileostomy closure—'I have had dreadful anterior resection syndrome symptoms ever since my stoma reversal a year ago… every day is a challenge…I can't get a job because of … unpredictability of visits to the loo' (www.Macmillan.org.uk), and the frustration of long delays to closure—'I am still bloody waiting for my reversal! Next week will be 5 months since I was told I was on the waiting list…it's over a year since my op now…I cannot book holidays…'

The study design and proposal has involved PPI. First, the original study concept and design has been informed by qualitative interviews of patients with LARS undertaken by the host unit.[5] Second, the 'Involving People' network have approved the project and will provide continued input; the design and lay summary have been peer reviewed by the University of Edinburgh Patient and Public Involvement Advisor and lay volunteer. Finally, the study question and design has been reviewed by a patient of SP who has reported that 'this debilitating condition (LARS), and the reasons why it occurs are investigated'…'people believe that when they are told they are clear of Cancer that everything will be okay and back to normal. That is far from the truth as we know.' This patient will continue to advise on study design and dissemination.

Patients will be included on steering committees and in consensus-seeking groups in the development of best practice guidelines. During this phase, we will ask patients how and when they believe reversal should be discussed and undertaken. We know that prior work has demonstrated timely closure when operation dates are given at index discharge,[14] yet given the distress and upheaval

following the index surgery this may not be appropriate. We will ask patients if they want to see the surgeon in clinic first (which may delay reversal), or whether timely reversal is more important.

The Dukes' Club has close links with various local and national patient liaison groups, including 'Involving people' and the ACPGBI patient liaison group—both of whom have already agreed to provide meaningful PPI at every stage of the study from final design to analysis and future direction. To achieve our final aims, we will ask patients to promote findings from the research, to raise awareness of the impact of delayed closure and guidelines for the best practice. Full patient engagement and promotion will be critical to ensuring derived best practice guidelines are widely accepted and implemented.

ETHICS AND DISSEMINATION

As the proposed methodology is of observational data collection only, with anonymised data shared with the lead research site, the committee was satisfied that informed consent of participants was not required.

The results from this study will be widely disseminated to the scientific and clinical community as well as patient groups through ties to the ACPGBI and other patient focused groups and charities via social media, email and print newsletters. We would expect results from the study to be presented at national and international level and to be published in a high-impact scientific journal with open access. Crucially, we intend that results will be used to inform consensus guidelines on optimum treatment pathways following ileostomy formation. Guidelines will be widely presented with a view to national implementation and the ultimate aim of improving the bowel function and overall quality of life of patients treated for rectal cancer. For some, these guidelines will affirm current practice, while for other units, the guidelines will provide a framework to overcome barriers to a timely ileostomy closure.

LIMITATIONS

This is an observational study and thus cannot derive causality from the collected data, although causality may be inferred from strong significant observed associations. We acknowledge that there is a risk of selection bias, as centres with known long waiting time to ileostomy closure may not sign up to the study or may omit patients where a long delay has occurred. However, we are requesting that consecutive cases be submitted to reduce selection bias and plan to cross-reference both case numbers and median delay with data collected centrally by the National Bowel Cancer Audit.

SIGNIFICANCE AND OUTLOOK

The study group believes that focusing on the treatment of cancer, and on the after-effects of cancer survivorship is critical in improving outcomes for patients with cancer. This belief mirrors that of the cancer survivorship document produced by the Department of Health.[3] Through ascertaining the severity of the problem, that is, how long the delays are, and by investigating barriers to timely closure, (including clinical and management protocols, service provision issues, etc), we will develop consensus guidelines on optimum treatment pathways following ileostomy formation. These guidelines would aim to streamline patient care and minimise delay to ileostomy closure, and potentially improve bowel function and overall quality of life of patients treated for rectal cancer in the UK. We believe that there will be both the necessary enthusiasm and resource allocation to embrace changes proposed from the current study. As such changes are accepted and implemented, future work will aim to explore the impact of such changes on time to closure and most importantly patient outcomes.

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Contributors PGV-S: wrote study protocol, designed data collection CRF and REDCap CRF, drafted manuscript. KG: wrote funding application and study protocol, designed data collection, drafted manuscript. KA, AEV, JT and SAP: critiqued funding application and study protocol, critiqued manuscript. JAC: conceived study, wrote ethics application, critiqued funding application and study protocol, critiqued manuscript.

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Competing interests None declared.

Patient consent Not required.

Ethics approval The study has been approved by the South West—Exeter Research Ethics Committee (18/SW/0024) and the Health Research Authority.

Provenance and peer review Not commissioned; externally peer reviewed.

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