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Renal impairment after ileostomy formation: a frequent event with long term consequences

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What does this paper add to the literature?

Dehydration is a common complication from ileostomy. However, the impact on renal function is poorly described. We demonstrate that ileostomy is an independent risk factor for postoperative renal impairment. This persists after ileostomy closure with a 2.2-fold increase in rates of new or worsening chronic kidney disease compared with patients without ileostomy.

Abstract

Aim: High stoma output and dehydration is common following ileostomy formation. However, the impact of this on renal function, both in the short term and after ileostomy reversal, remains poorly defined. We aimed to assess the independent impact on kidney function of an ileostomy after rectal cancer surgery, and subsequent reversibility after ileostomy closure.

Methods: This retrospective single-site cohort study identified patients undergoing rectal cancer resection from 2003-2017, with or without a diverting ileostomy. Renal function was calculated preoperatively, before ileostomy closure, and six months after ileostomy reversal (or matched times for patients without ileostomy). Demographics, oncological treatments, and nephrotoxic drug prescriptions were assessed. Outcome measures were deterioration from baseline renal function and development of moderate/ severe chronic kidney disease (CKD≥3). Multivariate analysis was performed to assess independent risk factors for postoperative renal impairment.

Results: 583 of 1213 patients had an ileostomy. Postoperative renal impairment occurred more frequently in ileostomates (9.5% absolute increase in rate of CKD≥3; P<0.0001) versus no change in patients without an ileostomy (P=0.757). Multivariate analysis identified ileostomy formation, age, anastomotic leak and renin-angiotensin-system inhibitors as independently associated with postoperative renal decline. Despite stoma closure, ileostomates remained at increased risk of progression to new or worse CKD (74/438 [16.9%]) compared to patients without an ileostomy (36/437 [8.2%], P=0.0001, OR 2.264 [1.49 to 3.46]).

Conclusions: Ileostomy formation is independently associated with kidney injury, with an increased risk persisting after stoma closure. Strategies to protect against kidney injury may be important in higher risk patients (elderly, receiving renin-angiotensin system antihypertensives, or following anastomotic leakage).

Introduction

Total mesorectal excision (TME) with sphincter-preservation is increasingly offered for rectal cancer resection[1]. However, a distal rectal anastomosis is accompanied by significant risk of leakage[2] associated with increased morbidity and mortality and adverse oncological outcomes[3-6]. A diverting stoma reduces the consequences of anastomotic leakage[7-12], with loop ileostomy widely advocated as a routine part of TME procedures[13].

A diverting loop ileostomy is itself associated with significant potential morbidity. Readmissions are common[14], with dehydration and electrolyte imbalance resulting from the high stoma output[15]; the cause in 40-43% of patients [14, 16-18]. There have been few studies examining changes in renal function while an ileostomy is *in situ*[19-21]. Only one, a small study with limited controls, attempted to characterise the impact from ileostomy formation [21]. This study highlighted a 10-fold increase in readmissions with acute kidney injury for patients with an ileostomy *in situ*, but also an increased risk of developing severe chronic kidney disease (CKD stage 4) at twelve months. This was a diverse patient group, with a heterogenous control cohort, making it difficult to separate the impact of ileostomy on renal function versus adjuvant, neoadjuvant or palliative treatments.

Even transient impairments in renal function may impact on long-term outcomes. A temporary decline in renal function (particularly perioperatively) has been shown to be an independent prognostic predictor for the later development of CKD[22, 23]. Lower estimated glomerular filtration rate (eGFR) is associated with an increased risk of hospitalization, cardiovascular events, and death[24-26], with even small increases in serum creatinine having adverse prognostic significance[27].

This study set out to evaluate whether creation of an ileostomy is an independent risk factor for post-operative renal impairment after rectal resection, and to define the impact this may have on kidney function following ileostomy reversal.

Methods

Patients

This retrospective cohort study was performed at a single, high-volume, tertiary referral centre in the United Kingdom. Patients were identified from a prospectively-collected registry for all rectal cancer resections from January 2003 to March 2017. Patients undergoing elective rectal resection with primary anastomosis and formation of an ileostomy (total mesorectal excision and loop ileostomy: TME/LI) were identified along with comparison cohorts undergoing rectal resection without ileostomy: high anterior resection without ileostomy (HAR) or abdominoperineal excision of the rectum (APR). For the purposes of this study, patients were allocated to TME/LI or HAR based on the presence or absence of an ileostomy and were independent of tumour or anastomotic height. Exclusion criteria were: pathology other than rectal adenocarcinoma; sigmoid colonic cancer; patients undergoing extended, multivisceral or simultaneous segmental colonic resections; and patients undergoing surgery for recurrent rectal cancer. Patients undergoing Hartmann's procedure were specifically excluded as in our institution this is reserved for the frailest patients (too unfit for reconstruction or abdominoperineal resection) or for emergency resections. Patients undergoing neoadjuvant radiotherapy underwent either short-course preoperative radiotherapy (SCRT, 25Gy over five days) or long-course chemoradiotherapy (LCCRT, 45Gy over five weeks with a concomitant radiosensitizer), in keeping with contemporaneous guidelines. Neoadjuvant systemic chemotherapy and first-line adjuvant chemotherapy was 5-fluorouracil and oxaliplatin. Institutional and ethical approval was obtained (IRAS/REC reference 18/NI/0138; University of East Anglia Faculty of Medicine and Health Sciences REC 2017/18-90SE).

Data Collection

Demographic and postoperative care data were retrieved from electronic notes and databases, and included anastomotic leakage, returns to theatre, and discharge medications (non-steroidal anti-inflammatory drugs, anti-hypertensives, metformin and other antidiabetic medications, proton-pump inhibitors). Antidiabetic and antihypertensive medications were used as surrogate markers of diabetes mellitus and hypertension respectively. Chemotherapy or radiotherapy regimens were recorded, as were unplanned readmissions within a year postoperatively.

Renal function

Serum creatinine levels were extracted from routine blood tests taken in outpatient clinics or primary care; in-patient results were excluded. Preoperative blood tests were used as a baseline (T_0). For patients undergoing neoadjuvant chemo(radio)therapy, these were taken after completion of neoadjuvant therapy. For TME/LI patients who underwent ileostomy closure, serum creatinine was abstracted immediately prior to ileostomy closure (T_1). Pilot data suggested median time to ileostomy closure was approximately six months after rectal resection[28]. Therefore, for comparison in HAR and APR patients (and TME/LI patients who did not undergo ileostomy closure), T_1 was taken as 6-months after rectal resection, coinciding with routine surveillance blood tests. Results were included in analysis when they fell within three months of the calculated follow-up dates (preoperatively for baseline or before ileostomy closure). Finally, follow-up renal function (T_2) was assessed 6-months following ileostomy closure (TME/LI) or 12-months after rectal resection (HAR and APR) respectively.

Estimated glomerular filtration rate (eGFR) was calculated de novo from creatinine assay results using the CKI-EPI (Chronic Kidney Disease Epidemiology Study) equation[29-32], as earlier cohorts used different equations for estimating eGFR. CKD stage was graded by Kidney Disease Improving Global Outcomes 2012 guidelines[30-32] [CKD stage 3 (CKD3) eGFR 30 to <60mL.min.1.73m^2; CKD4 15 to <30mL.min.1.73m^2; and CKD5 as <15mL.min.1.73m^2.

Outcomes

The main outcome measure was absolute change in eGFR at postoperative timepoint T_1 compared to the preoperative (T_0) baseline. Secondary outcomes were long-term development of moderate/ severe CKD (CKD≥3: eGFR<60 mL.min.1.73m^2) and severe CKD (CKD≥4: eGFR<30 mL.min.1.73m^2). Finally, percentage changes in eGFR between T_0 and T_1 were assessed, as trajectory is increasingly recognised as an important marker of long-term outcome[33-36]. Pilot studies demonstrated that approximately one-fifth of patients had a deterioration of greater than 20% ($\Delta eGFR_{-20\%}$) from preoperative baseline[28] and this was therefore taken as a threshold for most severe postoperative renal impairment as a method of converting continuous data to categorical data.

Statistics

For simple descriptive statistics between cohorts, t-tests and chi-squared tests or one-way ANOVA were used. For initial assessments of the impact of ileostomycreation on changes in postoperative eGFR, univariate and then multivariate regression analysis was performed. Absolute changes in eGFR were used as the dependent variable. For multivariate regression analysis, all factors with P<0.2 on univariate analysis were included.

Statistical analysis was performed using Stata 12.1 (StataCorp, Texas, USA), and graphical data presented using GraphPad Prism 7 (La Jolla, CA). Statistical significance was taken as P<0.05.

Results

Patient demographics

1213 patients were included in this study. 753 (62.1%) were male and the median age was 69.4 years (range 24.5-91.1). 583 (48.1%) patients had a loop ileostomy fashioned as part of the primary procedure (TME/LI), while 630 had no ileostomy formed (HAR: 364 patients and APR: 266 patients). No patient underwent defunctioning colostomy. Patient characteristics differed between cohorts, with the TME/LI cohort composed of younger patients (P<0.001) and more males (67.9%, P<0.001). There were differences in preoperative (baseline) renal function (P=0.002), with a lower proportion of patients with CKD≥3 undergoing TME/LI surgery (13.4%) compared to those undergoing HAR or APR (19.0%). There were subtle differences in tumour stage, with a lower proportion of Dukes B (stage II) tumours in patients undergoing TME/LI. Patients undergoing APR had a higher rate of node-negative disease compared with TME/LI and HAR (73.7% versus 63.6% and 61.8%, P=0.001), which may be as a consequence of higher rates of prior neoadjuvant (chemo)radiotherapy. Anastomotic leak rates were higher after TME/LI (11.0%) compared to HAR (5.2%, P=0.002). The demographic data are summarised in **Table 1**.

Ileostomy Closure

Ileostomy closure was performed in 494 of 583 patients (84.7%), with a further three patients (excluded from further analysis) undergoing closure at another institution on an unknown date. The remaining 86 patients were censored due to death (56 patients) or end of follow-up (30 patients) to 1st July 2018. 50% of all TME/LI patients underwent closure by 217 days post-operatively, with 77.9% closure at 1 year post-operatively (**Figure 1**). For those patients who did undergo closure, median time to closure was 189 days (mean 227 days, interquartile range 119 to 291 days).

Readmissions

Data on unplanned or emergency readmissions within one year of rectal resection were available in 869/1213 patients (data unavailable prior to 2007). 226/869 (26.0%) patients had any unplanned readmission within a year of surgery. 134/426 (31.5%) patients undergoing ileostomy formation underwent at least one unplanned readmission in the year after surgery compared to 92/443 (20.8%) patients without ileostomy (P=0.0004, OR 1.75 [1.29-2.37]). Subgroup analysis of patients without ileostomy showed readmission was more common following APR (48/177 [27.1%]; P=0.330 vs TME/LI

cohort) rather than HAR (44/266 [16.5%]; P<0.0001). Many patients experienced multiple readmissions, and mean number of readmissions was 0.47 readmissions per patient for TME/LI versus 0.21 and 0.39 for HAR and APR respectively.

Impact of ileostomy on postoperative renal function and chronic kidney disease

Renal function data were available to calculate both preoperative (T_0) and postoperative (T_1) eGFR for 1058 (87.2%) patients (TME/LI 561 patients; HAR 288; APR 209). The median time interval between T_0 and T_1 was 182 days with no difference between the three cohorts (P=0.523).

There was a significant postoperative decline in eGFR in ileostomates between T_0 and T_1 (78.3±0.68 vs 73.9±0.83 mL.min.1.73m^2; P<0.0001 paired t-test). No such decline was seen in patients without ileostomy or on subgroup analysis of HAR or APR patients (P>0.401). There was also a significant postoperative increase in proportion of patients with CKD ≥3 (**Table 2**, 13.4% to 23.0%, P<0.0001), again, not observed in patients without ileostomy (18.8% to 17.9%, P=0.757), including subgroup analysis of HAR and APR patients (P≥0.620). Similarly, presence of ileostomy increased incidence of post-operative severe CKD (CKD≥4) by 12.7-fold (P=0.0012), as compared to no change following rectal resection without ileostomy (P>0.999).

Clinically significant declines from baseline renal function ($\Delta eGFR_{-20\%}$) were more frequently observed in patients with ileostomy, occurring in 97/561 (17.3%) compared 32/497 (6.4%) patients without ileostomy (P<0.0001). The odds ratio of $\Delta eGFR_{-20\%}$ after ileostomy was 3.04 (1.99-4.69) versus patients without an ileostomy (P<0.0001). There was no difference between APR and HAR (P=0.460).

Risk factors for development of postoperative renal impairment

Univariate analysis identified increased age, higher preoperative eGFR, ileostomy formation and anastomotic leakage as correlated with absolute decline in eGFR at T_1 compared to preoperative (T_0) baseline (**Table 3**, P<0.001). ASA grade and prescription of renin-angiotensin system inhibitors on discharge were also correlated with a post-operative decline in eGFR at T_1 (P<0.05). Adjuvant chemotherapy was associated on univariate analysis with a post-operative improvement in eGFR (P=0.001).

In multivariate analysis, ileostomy formation remained independently associated with decline in eGFR, contributing an absolute 5.3 mL.min^{-1}.1.73m^2 decline in eGFR (P<0.001, **Table 3**). Increased age, higher

preoperative eGFR, postoperative anastomotic leak and renin-angiotensin system were also independently associated with an absolute postoperative decline in eGFR (P<0.05). As there was a relatively high proportion of missing data for discharge medications (707 patients included in multivariate analysis), analysis was repeated excluding drugs from the multivariate analysis (926 patients included). This did not change the variables independently associated with postoperative renal impairment. Adjuvant chemotherapy was not associated with post-operative changes in eGFR on multivariate analysis, suggesting this represented confounding biases from other variables.

Impact of postoperative renal impairment on long-term renal function

Blood tests were available at both T_0 and T_2 in 875 patients, with T_2 a median of 383 days after original surgery. In patients who previously had an ileostomy, there was an absolute increase of 14.9% in rates of CKD≥3 (**Table 2**, 28.4% versus 13.4% preoperatively), compared to an absolute increase of 7.0% in patients who had never had an ileostomy. When considering changes in CKD stage, 74/438 (16.9%) of patients previously undergoing ileostomy formation developed new CKD or progressed to a worse CKD stage, compared to 36/437 (8.2%) in patients who had never had ileostomy (P=0.0001, OR 2.264 [1.49 to 3.46]).

The impact on long-term renal function, of a decline >20% in baseline renal function at T_1 (ΔeGFR$_{-20\%}$), was assessed in 818 patients where data were available for all three time-points. These patients were particularly at risk of developing moderate or severe CKD: risk of CKD≥3 at T_2 was significantly increased (OR 6.89 [4.44-10.8], P<0.0001) in patients who previously experienced >20% decline in baseline renal function, while risk of severe CKD (CKD≥4) was also significantly increased (OR 7.44 [2.74-20.1], P=0.0003).

Discussion

In this study, we confirmed that ileostomy formation was independently associated with postoperative renal impairment after rectal resection. Other independent risk factors included increasing age, anastomotic leakage and prescription of renin-angiotensin system-inhibitors. Adjuvant chemotherapy was associated with postoperative improvements in eGFR. This was only seen on univariate (not multivariate) analysis, and therefore is likely to be due to other biases. It may further be a marker of patient selection, and of closer post-operative monitoring with admissions or fluid therapy in cases with evidence of renal impairment. While on crude analysis of mean eGFR data, this may appear to be a trivial decrease in eGFR (mean 4.4mL.min^{-1}.1.73m^2), it belies a very significant decrease in eGFR (>20% decline from baseline) in approximately one-fifth of patients undergoing ileostomy formation. This renal impairment persists following ileostomy closure, with subsequent development of moderate or severe CKD in 61% of such patients.

While these modest declines in renal function may seem of little clinical significance to the practicing colorectal surgeon, even small declines in kidney function have marked effect on long-term outcomes, particularly cardiovascular mortality[24, 37-39]. Longitudinal population studies have demonstrated patients with CKD3b (eGFR 30-44mL.min.1.73m^2) have a 1.8-fold increase in all-cause mortality compared to patients with eGFR >60mL.min.1.73m^2, while for CKD4 and CKD5 patients this increases to 3.2- and 5.9-fold respectively[24]. Risk is not confined to patients with established CKD: differences in renal function even within the bounds of 'normal' kidney function influence cardiovascular mortality with a 2.6-fold increase in patients with eGFR 60-75mL.min.1.73m^2 compared to patients with eGFR >104mL.min.1.73m^2[40]. Strategies such as electrolyte drinks, which have been demonstrated to prevent renal impairment following ileostomy formation, should now be evaluated further to assess impact on short-term and late renal function[41].

Although complications from ileostomy (particularly high-output stomas) have long been recognised clinically, this is poorly described in the literature. We confirm increased readmissions following ileostomy formation compared to resections without loop ileostomy. We found similar rates of readmission following abdominoperineal resection compared to rectal resections with ileostomy. While an analysis of the cause of readmission is beyond the scope of this paper, readmissions following APR are likely largely due to perineal wound complications[42], as compared to readmissions following ileostomy formation

where dehydration is the leading aetiology[16]. Any complications in the early postoperative period (particularly readmissions or renal impairment) may influence rectal cancer outcomes, through delays leading to early abandonment of, or not starting, adjuvant chemotherapy regimes[43-45].

There are few previous studies which define the impact of ileostomy formation on postoperative renal function. One previous report described a cohort of ileostomates, noting a post-operative mean eGFR decline of 6mL.min.1.73m^2, comparable to our population[19]. However, as a single cohort of mixed pathologies, it could not differentiate ileostomy-related renal impairment from other causes such as adjuvant chemotherapy or inflammatory bowel disease. A second study, using propensity-matching in a small cohort to demonstrate the effect of ileostomy formation, was strongly associated with renal impairment and subsequent progression to CKD4[21]. However, this study was limited by a high rate of surgery for palliation in the ileostomy cohort and a near-exclusively male population.

These limitations are highlighted by the differences observed here in demographics, tumour and treatment factors observed between cohorts. Significant (albeit small) differences were observed in preoperative eGFR, with better preoperative renal function seen in patients undergoing rectal resection with ileostomy compared to HAR or APR. These latter cohorts had significantly more patients with preoperative moderate or severe CKD. This likely reflects surgeon decision-making in that patients with advanced comorbidity ,or patients with a distal cancer, may be treated with an APR rather than undergo a low pelvic anastomosis. There were significant differences in neoadjuvant treatment between cohorts: disease stage is likely to have influenced both neoadjuvant therapy and in turn the surgical procedure. Furthermore, perception that neoadjuvant chemoradiotherapy increases anastomotic leakage makes ileostomy formation more likely. Distal tumours are at an increased risk of circumferential margin encroachment, and therefore more likely to receive neoadjuvant chemoradiotherapy. Irradiation of the sphincters is a relative contraindication to sphincter-preservation, and such patients may be offered APR rather than reconstruction. Age, gender, previous sphincter injury or incontinence, and perceived risk of subsequent development of systemic disease, may all influence surgeon decision-making regarding reconstruction versus APR. We noted significantly earlier pathological disease stage in patients undergoing APR rather than TME/LI, which may reflect the higher rates of neoadjuvant treatments. Anastomotic leakage was more frequent in the ileostomy cohort than in the non-ileostomy cohort, and although this was addressed by multivariate analysis, it is possible that the contribution from ileostomy

has been overestimated. Conversely, pelvic or perineal sepsis is common after APR and has not been accounted in this study.

A few aspects of the methodology require comment. The use of a threshold 20% decline in renal function as an endpoint reflects increasing calls to adopt such a strategy[33, 34] and is in keeping with previous studies[35, 36]. Percentage change based on single sample assays at each time-point is less precise than multiple measures, while lack of urinary albumin data limit interpretation of CKD states. Ideally, renal function at any time point should be assessed on two consecutive samples, but not feasible in such a retrospective cohort study. This would exclude the possibility that a significant decline in renal function was due to an erroneous pre- or post-operative eGFR estimate. The former seems unlikely as there was no difference in pre-operative eGFR between patients who did or did not subsequently develop renal impairment. Any estimate of eGFR from serum creatinine is subject to errors. CKI-EPI equation performs better than the Modification of Diet in Renal Disease Study (MDRD) equation in predicting mortality and end-stage renal disease[46, 47]. Changes in body mass composition, particularly in patients undergoing major catabolic and functional changes (for example, following anastomotic leakage), may influence creatinine levels and therefore eGFR. As patients in the ileostomy cohort are more likely to have anastomotic leakage, this may be a source of bias. However, in most patients, body composition would be expected to have normalised at six-months post-operatively. Furthermore, post-operative muscle loss would tend to overestimate eGFR by reducing creatinine, reducing apparent postoperative renal impairment. Finally, although we are not aware of changes in the laboratory creatinine assay, it is possible this has happened over the extended study period. As each post-operative blood tests are related to pre-operative tests, only a very small number of patients (in both ileostomy and no ileostomy cohorts) would be affected.

Data on the height of the tumour and of the colorectal anastomosis were not collected; all sphincter-preserving rectal resections where an ileostomy was formed were allocated as TME/LI cases. Patients were prospectively recorded on institutional databases as being either rectal or sigmoid cancer, and the latter excluded on that basis. While there may have been some errors in coding, with some proximal rectal cancers recorded as sigmoid cancers, or vice versa, it is unlikely that inclusion of a small number of distal sigmoid cancers in this dataset would to be a significant confounding factor with regards renal function outcome measures. We similarly do not have data on use of ureteric stents, although these would only routinely be used for extended resections (excluded from the analysis).

Our cohort is noteworthy by the lack of ethnic diversity, reflecting the local demographic. The incidence of renal injury following cardiac surgery appears to differ among ethnic groups[48]; whether this is the case for patients undergoing rectal cancer surgery is unknown. One should bear this in mind when generalizing the results from this study to non-Caucasian or mixed ethnicity populations. Finally, while most patients will have received mechanical bowel preparation prior to colonoscopic evaluation, patients undergoing planned TME/LI would routinely be prescribed a second, pre-operative mechanical bowel preparation, while those undergoing APR or HAR may not, with an enema used in some circumstances. This could be viewed as an independent cause of the renal impairment, rather than the ileostomy. However, previous studies, including a report from our own institution, have not consistently demonstrated bowel preparation is associated with renal impairment [49-51]. Many of these issues are inherent problems in a retrospective single-centre study covering an extended time period, and, as such, these findings need validation in a multicentre prospective setting.

In summary, this study demonstrates that ileostomy formation is independently associated with kidney injury occurring while the ileostomy is *in situ*. This kidney injury persists with long-term follow-up, even after ileostomy reversal. This highlights that ileostomy formation is not without risk, and that the thresholds for forming an ileostomy should be set accordingly, especially in lower-risk left-sided anastomoses. Impact on renal function has not been considered in recent trials evaluating early ileostomy closure but may be an additional benefit[52]. Careful monitoring of renal function in the post-operative period (particularly in higher risk patients such as older patients and those taking renin-angiotensin system-inhibitors) may allow earlier identification of kidney injury, and the opportunity to implement intervention such as oral rehydration salts [41] or prioritising early closure.

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| | Ileostomy | No Ileostomy | Total | P | "No Ileostomy" Subgroups | |
					HAR	APR
	n=583	n=630	n=1213		n=364	n=266
Median Age (Interquartile Range)	67·7 (61·0-74·1)	70.9 (62.5-77.9)	69·4 (61·8-75·9)	<0.0001	71·0 (62·2-78·1)	70·9 (63·9-77·8)
Male sex (%)	396 (67·9)	357 (56.7)	753 (62·1)	<0.0001	204 (56·0)	153 (57·5)
Preoperative eGFR ± S.D.	78·2 ± 17.1	75.2 ± 16.1	76·6 ± 16.7	0.002	74·9 ± 17.3	75·6 ± 16.9
ASA Grade (%)						
1	71 (12·2)	66 (10.5)	137 (11·3)		44 (12·1)	22 (8·3)
2	370 (63·5)	374 (59.4)	744 (61·3)		213 (58·5)	161 (60·5)
3	74 (12·7)	101 (16.0)	175 (14·4)	0.231	57 (15·7)	44 (16·5)
4	2 (0·3)	4 (0.6)	6 (0·5)		2 (0·6)	2 (0·8)
Not recorded	66 (11·3)	85 (13.5)	151 (12·5)		48 (13·2)	37 (13·9)
Tumour Dukes' stage (%)						
A [pT0-2 N0]	207 (35·5)	198 (31.4)	405 (33·4)		100 (27·5)	98 (36·8)
B [pT3-4 N0]	164 (28·1)	223 (35.4)	387 (31·9)	0.025	125 (34·4)	98 (36·8)
C [pT0-4 N1+]	212 (36·4)	209 (33.2)	421 (34·7)		139 (38·2)	70 (26.3)
Anastomotic leaks (%)	64/583 (11·0)	19/364 (5·2)	83/947 (8·8)		19/364 (5·2)	-
Grade A	5 (0·9)	-	5 (0·5)	0.002	-	-
Grade B	38 (6·5)	5 (1·4)	43 (4·5)		5 (1·4)	-
Grade C	21 (3·6)	14 (3·8)	35 (3·7)		14 (3·8)	-
Neoadjuvant Treatment (%)						
Systemic chemotherapy	25 (6·0)	37 (5.9)	72 (5·9)	0.211	6 (1·7)	31 (11·7)
Radiotherapy	131 (22·5)	168 (26.7)	299 (24·7)	0.090	38 (10·4)	130 (48·9)
Short course radiotherapy	*35 (6·0)*	*51 (8.1)*	*86 (7·1)*	*0.156*	*1 (0·3)*	*50 (18·8)*
Long course chemoradiotherapy	*96 (16·5)*	*116 (18.4)*	*212 (17·5)*	*0.373*	*37 (10·2)*	*79 (29·7)*
Contact radiotherapy	*0*	*1 (0.2)*	*1 (0·1)*	*0.336*	*0*	*1 (0·4)*
Adjuvant Treatment (%)						
Systemic chemotherapy	200 (34·4)	183 (29.0)	383/1213 (31·6)	0.049	119 (32·7)	64/266 (24·1)
Radiotherapy	6 (1·0)	10 (1.6)	16/1213 (1·3)	0.395	2 (0·6)	8/266 (3·0)

Table 1.   Demographic data for patients undergoing diverting loop Ileostomy versus comparison cohorts not undergoing loop ileostomy. Demographic data for the whole population, and the two cohorts of patients stratified by presence or absence of ileostomy. For reference, the demographic data for the two subgroups of patients without ileostomy (HAR and APR) are also shown.

Figures in parentheses are percentages. TME: rectal resection with primary anastomosis and diverting ileostomy; HAR: rectal resection with primary anastomosis without diverting ileostomy; APR: abdominoperineal resection; eGFR: estimated glomerular filtration rate; CKD: chronic kidney disease; S.D.: standard deviation; ASA: American Society of Anaesthesiologists grade

| Procedure | Time Point | No CKD | Moderate/ Severe CKD (CKD3+) | | | |
			CKD 3	CKD 4	CKD 5	Total
Ileostomy	**Preoperative (T0)**	**503/581 (86.6%)**	77/581 (13.3%)	1/581 (0.2%)	0	**78/581 (13.4%)**
	Postoperative (T1)	**433/562 (77.0%)**	117/562 (20.8%)	12/562 (2.1%)	0	**129/562 (23.0%)**
	Postoperative (T2)	**379/529 (71.6%)**	126/529 (23.8%)	15/529 (2.8%)	9/529 (1.7%)	**150/529 (28.4%)**
No Ileostomy	**Preoperative (T0)**	**508/627 (81.0%)**	111/627 (17.7%)	7/627 (1.1%)	1/627 (0.2%)	**119/627 (19.0%)**
	Postoperative (T1)	**406/497 (81.7%)**	86/497 (17.3%)	3/497 (0.6%)	2/497 (0.4%)	**91/497 (18.3%)**
	Postoperative (T2)	**411/555 (74.1%)**	127/555 (22.9%)	15/555 (2.7%)	2/555 (0.4%)	**144/555 (25.9%)**

Table 2. **Preoperative and postoperative rates of Chronic Kidney Disease (CKD) in ileostomy cohort and comparison cohort without ileostomy.** Data show rates of patients fulfilling eGFR criteria for each of the CKD stages for the time point measured.

T0 is preoperatively before rectal resection; T1 is prior to ileostomy closure for ileostomy cohort or a matched time at six-months after rectal resection for comparison cohort without ileostomy; T2 is six-months after ileostomy closure or a matched time at twelve-months after rectal resection for comparison cohort without ileostomy. CKD stage was graded by Kidney Disease Improving Global Outcomes 2012 guidelines[30-32] [CKD stage 3 (CKD3) eGFR 30 to <60mL.min.1.73m^2; CKD4 15 to <30mL.min.1.73m^2; and CKD5 as <15mL.min.1.73m^2

	Univariate Regression Coefficient (95% confidence interval) n=1058	P	Multivariate Regression Coefficient Discharge Medications Included (95% confidence interval) n=707	P	Multivariate Regression Coefficient Discharge Medications Excluded (95% confidence interval) n=926	P
Age	-0·14 (-0·22 to -0·07)	<0·001	-0·37 (-0·49 to -0·26)	<0·001	-0·35 (-0·44 to -0·26)	<0·001
Male sex	-1·20 (-2·72 to +0·32)	0·121	0·65 (-1·17 to +2·46)	0·486	0·30 (-1·29 to +1·89)	0·716
Preoperative eGFR	-0·13 (-0·17 to -0·08)	<0·001	-0·28 (-0·34 to -0·21)	<0·001	-0·24 (-0·30 to -0·19)	<0·001
Loop Ileostomy Formation	-4·83 (-6·28 to -3·37)	<0·001	-5·34 (-7·12 to -3·56)	<0·001	-5·00 (-6·53 to -3·48)	<0·001
ASA Grade						
1	1 (reference)		1 (reference)		1 (reference)	
2	-3·18 (-5·59 to -0·76)		-1·38 (-4·05 to +1·29)		-2·10 (-4·38 to +0·18)	
3	-4·38 (-7·37 to -1·39)	0·03	-2·22 (-5·74 to +1·30)	0·655	-3·05 (-5·93 to -0·18)	0·197
4	0·74 (-11·6 to +13·1)		0·03 (-16·33 to +16·39)		-0·47 (-11·9 to +11·0)	
Tumour Dukes' stage						
A [pT0-2 N0]	1 (reference)		1 (reference)		1 (reference)	
B [pT3-4 N0]	-0·65 (-2·50 to +1·21)	0·06	-1·74 (-3·92 to +0·45)	0·125	-0·83 (-2·73 to +1·07)	0·603
C [pT0-4 N1+]	1·46 (-0·34 to +3·25)		0·58 (-2·03 to +3·19)		0·04 (-2·25 to +2·32)	
Anastomotic leak	-6·62 (-9·57 to -3·66)	<0·001	-5·40 (-8·74 to -2·05)	0·002	-5·14 (-8·08 to -2·20)	0·001
Discharge Medications						
Insulin/ antihyperglyaemics	-2·00 (-4·14 to +0·15)	0·068	-1·01 (-3·06 to 1·04)	0·334	-	-
Antihypertensives	-1·82 (-3·72 to +0·08)	0·061	1·28 (-1·44 to +4·01)	0·357	-	-
NSAIDs	-1·54 (-3·75 to +0·67)	0·172	-0·41 (-2·54 to 1·72)	0·706	-	-
ACE/ AT2 inhibitors	-2·54 (-4·66 to -0·42)	0·019	-3·06 (-6·00 to -1·25)	0·041	-	-
PPIs	-0·74 (-2·68 to +1·20)	0·454	-	-	-	-
Neoadjuvant Treatment (%)						
Radiotherapy (SCRT/ LCCRT)	0·46 (-1·24 to +2·17)	0·594	-	-	-	-
Systemic chemotherapy	-0·50 (-3·61 to +2·61)	0·752	-	-	-	-
Adjuvant Treatment (%)						
Radiotherapy	2·02 (-4·24 to +8·29)	0·526	-	-	-	-
Systemic chemotherapy	2·55 (+1·00 to +4·11)	0·001	1·97 (-0·50 to +4·43)	0·117	1·38 (-0·72 to +3·48)	0·197

Table 3. Univariate and multivariate regression analysis showing impact of patient and operative factors on absolute changes in postoperative renal function, comparing postoperative renal function (T_1) with preoperative baseline at T_0.

eGFR: estimated glomerular filtration rate; ASA: American Society of Anaesthesiologists; NSAIDs: non-steroidal anti-inflammatory drugs; ACE: angiotensin-converting enzyme; AT2: angiotensin-2; PPIs: proton-pump inhibitors; SCRT: short-course radiotherapy; LCCRT: long-course chemoradiotherapy.

Figure 1. Distribution of timing of ileostomy closure.

Figure plots monthly number of ileostomy closures (Left axis and blue bars) and the cumulative closure rate (grey Kaplan-Meier curve and Right axis, vertical ticks- censor points).