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ORIGINAL ARTICLE

Intraoperative adverse events as a risk factor for local recurrence of rectal cancer after resection surgery

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Abstract

Aim: Failure to achieve a radical resection as well as intraoperative rectal perforation are important risk factors for local recurrence after rectal cancer surgery, but the importance of other intraoperative adverse events for the prognosis is unknown. The aim of this study was to assess the occurrence of intraoperative adverse events during rectal cancer surgery, and to determine whether these were associated with an increased risk of local recurrence.

Methods: A retrospective population-based cohort study was undertaken, including all patients in Region Västra Götaland, Sweden, who had undergone primary resection surgery for rectal cancer diagnosed between 2010 and 2014, registered in the Swedish Colorectal Cancer Registry. Data were retrieved from the registry and through review of the medical records.

Results: In total, 1208 patients were included in the study of whom 78 (6%) developed local recurrence during the follow-up period of at least 5 years. Intraoperative adverse events were common and occurred in 62/78 (79%) of patients with local recurrence compared to 604/1130 (53%) of patients without local recurrence. In multivariate analysis intraoperative adverse events were found to be an independent risk factor for local recurrence of rectal cancer, as were nonradical resection, a high pathological T stage, the presence of lymph node metastases, type of surgery and refraining from rectal washout during anterior resection and Hartmann's procedure.

Conclusions: Intraoperative adverse events were found to be an independent risk factor for local recurrence of rectal cancer and could possibly be used together with other known risk factors to select patients for intensified postoperative surveillance.

KEYWORDS
intraoperative adverse events, local recurrence, rectal cancer, risk factors

INTRODUCTION

Surgery is the primary curative treatment for rectal cancer, preceded by (chemo)radiotherapy in more advanced cases [1]. The aim of surgery for rectal cancer is to achieve a radical resection in order to reduce the risk of local recurrence and improve survival [2–6]. This is accomplished by removing the tumour together with surrounding lymph nodes enclosed by an intact mesorectal fascia [7].

Local recurrence of rectal cancer can be defined as the recurrence of cancer within the pelvis, alone or as part of a generalized disease [8, 9]. The frequency of local recurrence of rectal cancer has been steadily declining in recent years and is now below 10% [10–13]. Major factors for this improvement, as well as for the improved survival in rectal cancer, are improved surgical technique (total mesorectal excision, TME), and preoperative radiotherapy [14–18].

Known risk factors for local recurrence of rectal cancer include locally advanced tumours, number of positive lymph nodes and tumours located in the lower part of the rectum [9, 19–22]. Surgical risk factors include nonradical removal of the primary rectal tumour, and intraoperative rectal perforation [3–5, 9, 22–24]. In addition, rectal washout performed during anterior resection and Hartmann's procedure has been reported to reduce the risk of local recurrence [25, 26]. Furthermore, anastomotic leakage, a complication that may be due to technical difficulties, has been found to increase the risk of local recurrence [27–29].

Thus, the surgical technique is important in reducing the risk of local recurrence of rectal cancer. However, while rectal perforation during surgery has been shown to increase the risk of local recurrence, other intraoperative adverse events, and their possible association to local recurrence, have not been studied in detail. One study on intraoperative technical difficulties found this to be a risk factor for local recurrence of colorectal cancer, though limited to laparoscopic surgery and not looking at rectal cancer specifically [30]. The aim of this study was to investigate intraoperative adverse events during rectal cancer surgery as a possible risk factor for local recurrence.

What does this paper add to the literature?

This paper describes intraoperative adverse events in rectal cancer surgery in an unselected patient cohort, which has not been reported previously. It evaluated the association of intraoperative adverse events to local recurrence and its use as risk factor.

METHODS

Study population and data collection

A retrospective population-based cohort study was undertaken, including all patients in Region Västra Götaland, Sweden, who had undergone primary resectional surgery for rectal cancer diagnosed between 2010 and 2014, registered in the Swedish Colorectal Cancer Registry (SCRCR). This is a registry with high validity which was started in 1995, and 98.5% of all cases of rectal cancer in Sweden are registered [13]. Exclusion criteria in our study were local excision of the tumour or stoma creation without resection of the tumour.

Data on preoperative assessment, neoadjuvant therapy, surgical treatment and follow-up regarding local recurrence were retrieved from the SCRCR. Additional information was collected by review of the medical records using a predefined clinical record form. The surgical documentation was audited (by S.W. and B.S.), and each event that was not a step in the expected surgical procedure was noted and assessed in relation to the criteria defining intraoperative adverse events, see below. The presence or absence of local recurrence was verified through examination of the medical records.

Definitions and classification of intraoperative adverse events

Local recurrence of rectal cancer was defined as recurrence of cancer within the pelvis, confirmed by clinical examination, radiology and/or pathology.

There is no uniform classification of intraoperative adverse events although one has recently been suggested, however this was published after the completion of this study [31]. Intraoperative adverse events for this study were defined as any significant deviation from the standard surgical procedure, which was unforeseen and/or unintentional, and which significantly complicated the surgery, prolonged the duration of the surgery and/or negatively affected the way the surgery was executed.

The intraoperative adverse events were divided into nine different categories: bleeding, dissection difficulties, damage to the rectum, damage to other organs, problems with division of the rectum, problems with creation of an anastomosis, problems with creation of a stoma, difficulties due to anatomical factors, and others (Table 1). The events extracted from the medical records were compiled in a separate document, anonymised with only study-id for each patient, and containing no additional information. This was then reviewed independently by three of the authors (S.W., E.A. and E.H.), blinded to the local recurrence-status of each patient at this point. The decisions from each reviewer were compared, and disagreements were discussed to reach a consensus from which final criteria for each category were decided. This was done for all events with uncertainty and for all cases of bleeding, which was the category found most difficult to define. All events were then re-assessed against the criteria.

Statistical analysis

The size of the cohort of patients was restricted due to being limited to patients diagnosed from 2010 to 2014, rendering 1208 evaluable patients. A post hoc sample size calculation is presented in the Supplement (Appendix S1).

Group differences (local recurrence vs. no local recurrence) in patient characteristics were summarized and were quantified using effect size estimates. The reason for using effect size instead of *p*-values was to avoid the interpretation being too influenced by sample size. Since rectal cancer occur at a relatively high age, death is a competing risk to

TABLE 1 Adverse events

	Definition: any significant deviation from the standard surgical procedure, which was unforeseen and/or unintentional, and significantly complicated the surgery, prolonged the duration of the surgery and/or negatively affected the result the surgery.
Bleeding	Bleeding (at least one of the following): • described as heavy or extensive • that caused problems • located in unexpected anatomical sites, such as the kidney capsule, the v. iliaca etc • difficult to stop • requiring more than compression, diathermy, haemostatic products and/or a few sutures, such as clips or packing • requiring multiple (>2) methods of haemostasis • is of a volume ≥700 ml
Dissection difficulties	Difficult dissection described as arduous or time-consuming, due to for example adhesions or fibrotic tissue. Abdominal dissection described as driven to far or not far enough.
Damage to the rectum	Perforation or tear of the rectum. In cases of preoperative spontaneous perforation with abscesses this is included when the abscess is cross cut during surgery whereby an opening into the rectum is created.
Damage to other organs	Tear, perforation or damage from diathermy on any other organ but the rectum, for example the colon, small intestine, reproductive organs, spleen or urinary organs.
Problems with division of the rectum	Problems with linear stapling, for example problems reaching below the tumor, leakage form or perforation of the staple line and use of multiple staplers (>1 in open surgery and >3 in laparoscopic surgery) etc
Problems with formation of an anastomosis	Problems with circular stapling, need to mobilize the colon further after docking the circular stapler, resection of bowel that was intended for the anastomosis due to ischaemia or inflammation
Problems with creation of a stoma	Intra-abdominal problems with formation of a stoma, such as rotation of the bowel or the need to mobilize the bowel further due to tension after extraction through the abdominal wall
Anatomical factors	Arduous or time-consuming dissection due to anatomical factors that make visibility or access difficult
Conversion	Conversion from laparoscopic to open surgery
Other	Any other event that meets the definition of adverse event, for example unexpected change of surgical procedure performed, wrong preoperative diagnosis, lost surgical instruments, urine leakage into the abdominal cavity or anaesthesiological problems causing significant prolongation of surgery

local recurrence. The cumulative subdistribution hazard function was estimated for local recurrence as well as the competing event death, and competing risk regression was used for estimating the predicted cumulative incidence probability and 95% compatibility intervals [32].

A Cox proportional hazard model was used to assess whether intraoperative adverse events and other possible prognostic factors could be used to predict local recurrence. The modelling strategy was performed in steps where first, variable selection was performed using shrinkage estimation, and second, the effect of the selected variables was quantified by maximum likelihood estimation. The variables included in this analysis were, in addition to intraoperative adverse events, neoadjuvant therapy, type of surgery, rectal washout, pathological tumour stage, pathological lymph node stage and resection radicality. Type of surgery and the performance of rectal washout were combined and analysed as one variable, as rectal washout only is relevant for patients undergoing anterior resection or Hartmann's procedure. Comparisons were made between the different types of surgery regardless of rectal washout to reflect the predictive ability of type of surgery, and between anterior resection and Hartmann's procedure with and without washout to reflect the predictive ability of rectal washout. Missing values for these variables were imputed by single imputation k-nearest neighbours [33].

To optimize the predictive performance of the Cox model a least absolute shrinkage and selection operator (LASSO) strategy was used [34]. LASSO includes variable selection as well as regularization (shrinkage) to avoid model overfitting. The degree of shrinkage was established using 10-fold cross-validation where Harells C-index [35, 36] for the validation set was maximized, and the "one standard

error" rule was used for selection of the shrinkage parameter [34, 37]. Variable importance of each predictor was evaluated by resampling methods that involved all of the modelling steps, which ensured that the uncertainty was not underestimated [38]. Firstly, 1,000 bootstrap samples and out-of-bag-data (data not selected) were created, and the proportion of times (percentage of 1,000) each variable was selected by the LASSO strategy was evaluated. Secondly, the selected variables were used in an ordinary multiple Cox regression to estimate hazard ratios. Variable importance was then addressed by the percentages of times each variable was selected across the 1,000 samples, as well as the distribution of the estimated hazard ratios in the samples where the respective variables were included. The additional predictive within-sample performance achieved by adding intraoperative adverse events to the model (or the other variables) was addressed by the percentage change in likelihood ratio Chi-2 statistics and Nagelkerke pseudo R2 and Harrell's C-index.

Overall predictive performance was done by internal validation but where the overly optimistic bias (highly accurate predictions on the same data as the model was estimated on) was corrected for by bootstrapping techniques. The time-dependent AUC of Uno et al. was used where the value 0 and 1 suggested poor and perfect fit, respectively [39].

The agreement between predicted and observed risk for local recurrence was assessed by means of a calibration plot with bias corrected predictions based on bootstrapping. The extent to which a prediction model is calibrated is important as it addresses whether the predictions will give a correct perception of the observed risk across groups of patients.

The R software was used for these analyses, with the packages cmprsk and timereg for competing risk analysis, recipes for imputation, glmnetUtils and glm for estimation, rsample for bootstrapping and hdnom for prediction and calibration.

RESULTS

A total of 1,687 patients diagnosed with rectal cancer during the period 2010–2014 in the Region of Västra Götaland were identified in the Swedish Colorectal Cancer Registry. After exclusions, 1,208 patients who underwent surgery with resection were included (Figure 1). The median follow-up time after surgery was 70 months (range 0–116). All patients were followed for at least 5 years or until death. Seventy-eight patients (6%) developed local recurrence during the follow-up period. A total of 383 (32%) patients died. The cumulative incidence of local recurrence and all-cause mortality are presented in Figure 2.

Preoperative patient and tumour characteristics and neoadjuvant treatment

There was a moderate difference in distance from the anal verge to the tumour between patients with and without local recurrence, with a higher prevalence of low tumors in patients with local recurrence (Table 2). There were no other moderate or large differences between the groups in terms of preoperative patient and tumour characteristics or neoadjuvant treatment.

Surgical and histopathological characteristics

The difference in tumour height between the groups was reflected by a small difference in the type of surgical procedure performed (Table 3). Abdominoperineal excision was the most common operation in patients who developed local recurrence, while anterior

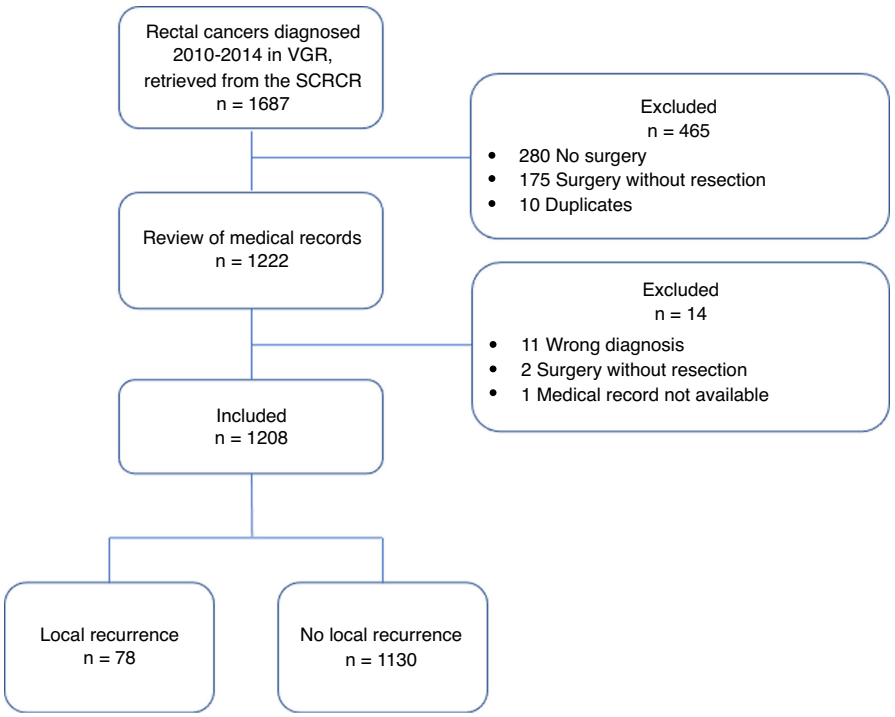

FIGURE 1 Study flowchart

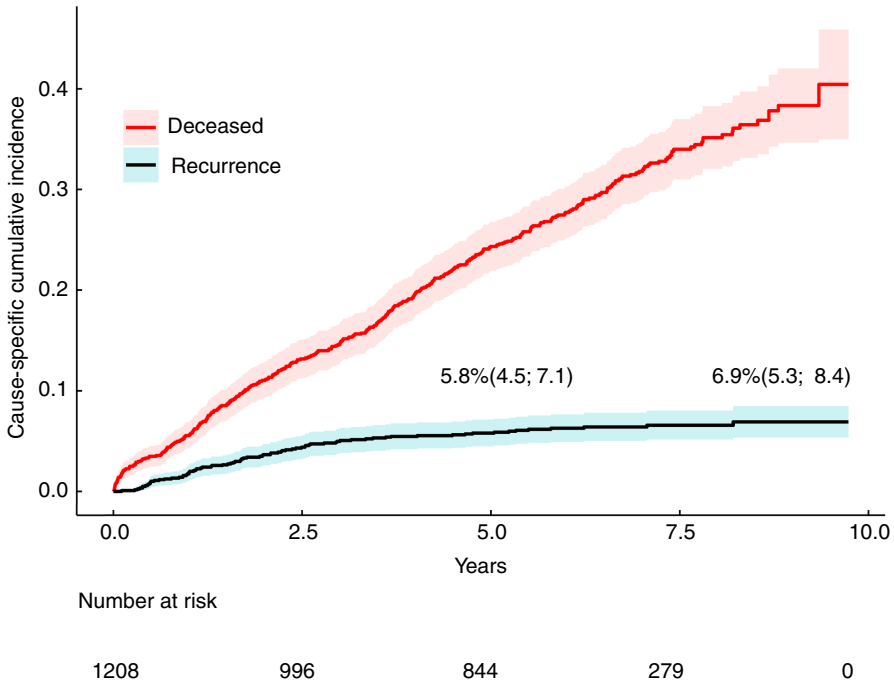

FIGURE 2 Cause-specific cumulative incidence with 95% compatibility intervals. Rates (%) at 5 and 10 years, respectively

resection was the most common in those who did not. Rectal washout in patients operated by anterior resection or Hartmann's procedure was performed in 24/44 (55%) of patients who developed local recurrence, compared to 610/719 (85%) of patients who did not. Patients who developed local recurrence more often had an advanced pathological tumour stage and positive lymph nodes, and a higher frequency of nonradical resection as judged microscopically.

Intraoperative adverse events

Intraoperative adverse events were present in 62/78 (79%) of patients who developed local recurrence, compared to 604/1130 (53%) of those who did not (Table 3). Of patients with an intraoperative adverse event 62/666 (9%) developed local recurrence, while the same number for patients without an intraoperative adverse event was 17/542 (3%) (Figure 3). The frequency of different categories of intraoperative adverse events are presented in Table 4. The main contributors to the higher overall occurrence of intraoperative adverse events in the local recurrence group were bleeding, damage to the rectum and conversion from laparoscopic to open surgery.

Variable importance

Important factors for predicting local recurrence were radical surgery, pathological tumour stage, lymph node metastases and intraoperative adverse events in terms of the percentage of times they were selected by the LASSO regression (99, 97, 94 and 77%, respectively), (Table 5, Figure S1). Furthermore, anterior resection as compared to Hartmann's procedure or abdominoperineal excision (96 and 63%, respectively), and the performance of rectal washout during Hartmann's procedure and anterior resection (74 and 57%, respectively) were found to be factors of importance in predicting local recurrence (Table 5, Figure S1). The greatest magnitude of effect on the risk for local recurrence measured by median hazard ratio had, in descending order, nonradical resection (HR 5.5), advanced pathological tumour stage (HR 4.7), anterior resection compared to Hartmann's procedure (HR 0.27) or abdominoperineal excision compared to anterior resection (HR 3.2), washout during Hartmann's procedure and anterior resection (HR 0.31 and 0.33, respectively), and intraoperative adverse events (HR 3.1).

Prediction of local recurrence

The median (Q1; Q3) time-dependent AUC at 5 year follow-up was 0.85 (0.84; 0.86). The calibration plot displays the bias corrected predictions versus actual rates. For patients with low risk of local recurrence, the model underestimated the risk, but for patients with higher risk, the predicted risk was overemphasized. By adding adverse events to the model, the predictions were slightly improved with the explanatory power increased by 11% (Figure 4). For example, the predicted risk of local recurrence within 5 years for an average patient with radical resection and without adverse event was 3.7%. With an adverse event, all other things being equal, predicted risk was 4.9%. With nonradical resection the risk was 15%.

DISCUSSION

Local recurrence is a dreaded outcome after surgery for rectal cancer. There are known risk factors, but the importance of an

TABLE 2 Preoperative patient and tumour characteristics and neoadjuvant treatment

	Total *n* = 1208	Local recurrence *n* = 78 (6%)	No local recurrence *n* = 1,130 (94%)	Effect size[a]
Gender				
Female	510 (42%)	33 (42%)	477 (42%)	0.00
Male	698 (58%)	45 (58%)	653 (58%)	
Age				
Median	69	69	70	0.04
Range	25–93	34–89	25–93	
BMI				
Median	25.3	25.1	25.3	0.02
Range	15.6–50.1	18.7–38.2	15.6–50.1	
Missing	10 (1%)	0 (0%)	10 (1%)	
ASA				
1	236 (20%)	17 (22%)	219 (19%)	0.02
2	718 (59%)	44 (56%)	674 (60%)	
3	238 (20%)	15 (19%)	223 (20%)	
4	9 (1%)	1 (1%)	8 (1%)	
Missing	7 (1%)	1 (1%)	6 (1%)	
Clinical T stage				
T1–2	292 (24%)	11 (14%)	281 (25%)	0.07
T3	669 (55%)	47 (60%)	622 (55%)	
T4	175 (14%)	16 (21%)	159 (14%)	
Missing	74 (6%)	4 (5%)	68 (6%)	
Clinical M stage				
M0	1,100 (91%)	70 (90%)	1,030 (91%)	0.01
M1	99 (8%)	6 (8%)	93 (8%)	
Missing	9 (1%)	2 (3%)	7 (1%)	
Tumour distance from anal verge (cm)				
0–5	319 (26%)	24 (31%)	295 (26%)	0.30
6–10	479 (40%)	35 (45%)	444 (39%)	
11–15	399 (33%)	17 (22%)	382 (34%)	
Missing	11 (1%)	2 (3%)	9 (1%)	
Neoadjuvant therapy				
Yes	769 (64%)	48 (62%)	721 (64%)	0.05
No	439 (36%)	30 (38%)	409 (36%)	

Abbreviations: ASA, American Society of Anesthesiologists physical status; BMI, body mass index.

[a]Effect size was calculated using Cohen's D for continuous variables (age, BMI and distance from anal verge), Cohen's H for binary variables (gender, clinical M stage and neoadjuvant therapy), and Cramer's V for variables with more than two categories (ASA and clinical T stage). For Cohen's D and H an effect size of <0.20 was considered small, 0.20–0.50 moderate and >0.50 large. Cramer's V range from 0 to 1 where 0, no association; 1, complete association.

uneventful surgery without intraoperative adverse events has not been widely studied. We found that intraoperative adverse events were to some extent associated with an increased risk of local recurrence, indicating that the surgical procedure itself is important for the outcome.

Intraoperative adverse events, by the definition used in this study, are common in rectal cancer surgery, and occurred during the operations on 666 out of 1,208 patients (55%), indicating the difficulty of these procedures. The higher prevalence of intraoperative adverse events found in patients who developed local recurrence could partially be explained by factors such as a more advanced tumour stage and a lower location of the tumour in the rectum making surgery more complicated. However, in the multivariable prediction models we found intraoperative adverse events to some extent

TABLE 3 Surgical and pathological characteristics

	Total $n = 1208$	Local recurrence $n = 78$	No local recurrence $n = 1130$	Effect size[a]
Surgical procedure				
Anterior resection	573 (47%)	21 (27%)	552 (49%)	0.12
Abdominoperineal excision	445 (37%)	34 (44%)	411 (36%)	
Hartmann's procedure	190 (16%)	23 (29%)	167 (15%)	
Surgical technique				
Open	847 (70%)	56 (72%)	791 (70%)	0.06
Laparoscopic	286 (24%)	14 (18%)	272 (24%)	
Conversion	72 (6%)	8 (10%)	64 (6%)	
Missing	3 (0%)	0 (0%)	3 (0%)	
Rectal washout[b]				
Yes	628 (84%)	24 (55%)	610 (85%)	0.68
No	123 (16%)	20 (45%)	109 (15%)	
Duration of surgery (min)				
Median	276	275	276	0.02
Range	76–903	110–813	76–903	
Missing	20 (2%)	0 (0%)	20 (2%)	
Highest surgical competence				
Resident/specialist	7 (1%)	0 (0%)	7 (1%)	0.16
Colorectal surgeon	1196 (99%)	78 (100%)	1118 (99%)	
Missing	5 (0%)	0 (0%)	5 (0%)	
Bleeding volume (ml)				
Median	350	500	350	0.37
Quartiles	150–750	200–1200	150–700	
Missing	71 (6%)	0 (0%)	71 (6%)	
Adverse events				
Yes	666 (55%)	62 (79%)	604 (53%)	0.56
No	542 (45%)	16 (21%)	526 (47%)	
Pathological T stage				
T0	30 (2%)	0 (0%)	30 (3%)	0.17
T1	62 (5%)	0 (0%)	62 (5%)	
T2	357 (30%)	7 (9%)	350 (31%)	
T3	668 (55%)	57 (73%)	611 (54%)	
T4	87 (7%)	14 (18%)	73 (6%)	
Missing	4 (0%)	0 (0%)	4 (0%)	
Pathological N stage				
N0	692 (57%)	22 (28%)	670 (59%)	0.16
N1	310 (26%)	29 (37%)	281 (25%)	
N2	202 (17%)	27 (35%)	175 (16%)	
Missing	4 (0%)	0 (0%)	4 (0%)	
Microscopically radical				
Radical	1139 (94%)	59 (76%)	1080 (96%)	0.61
Not radical	55 (5%)	17 (22%)	38 (3%)	
Not assessable/missing	14 (1%)	2 (3%)	12 (1%)	

[a]Effect size was calculated using Cohen's D for continuous variables (duration of surgery and bleeding volume), Cohen's H for binary variables (rectal washout, highest surgical competence, adverse events and microscopically radical), and Cramer's V for variables with more than two categories (surgical procedure, surgical technique, pathological T stage and pathological N stage). For Cohen's D and H an effect size of <0.20 was considered small, 0.20–0.50 moderate and >0.50 large. Cramer's V range from 0 to 1 where 0: no association, 1: complete association.

[b]Rectal washout only analysed for patients where this is relevant (anterior resection and Hartmann's procedure).

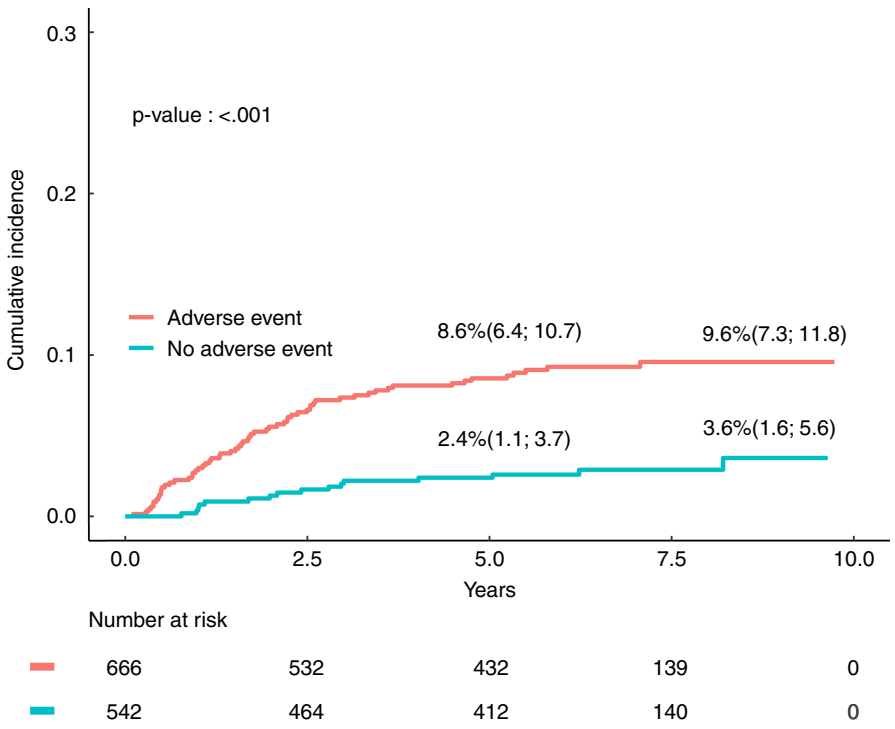

FIGURE 3 Cumulative incidence of recurrence estimated competing risk regression with 95% compatibility intervals

predicted local recurrence of rectal cancer, beyond covariation with these known risk factors. We could also see that known risk factors for local recurrence such as advanced tumour stage, radical resection and performance of rectal washout were important, which may indicate that we had a cohort similar to other cohorts of rectal cancer patients. It seems as if some adverse events, mainly damage to the rectum, bleeding and conversion from laparoscopic to open surgery, are more important than others regarding the association to local recurrence. However, the cohort was too small to allow for subgroup analyses.

The evaluation of the prediction model by extensive resampling showed a limited forecasting performance as demonstrated by the lack of calibration. Intraoperative adverse events did contribute to further explain the variation in outcomes in addition to the other factors, but the contribution was relatively modest and highly variable across samples.

Local recurrence of rectal cancer is associated with substantial suffering for the patients and increased consumption of health care resources [40, 41]. The prognosis is still poor, and surgery with curative intent is only possible in a minority of patients [42–44]. Since we found that the occurrence of intraoperative adverse events was an independent risk factor for local recurrence of rectal cancer, this could be used together with other risk factors as part of a prediction model to select patients with higher risk of local recurrence who could benefit from more intensive follow-up. This could lead to earlier diagnosis of local recurrences, probably resulting in a better prognosis for these patients [45, 46]. Some studies have failed to show that more intensive follow-up in general reduces the colorectal cancer-specific mortality [47], but it may be of value to focus these efforts on patients with an increased risk of local recurrence.

This study included an unselected consecutive population-based cohort, which is one of the main strengths. Our resampling-based strategy for evaluating variable importance and predictive performance ensures a high internal validity since it incorporates the uncertainty induced by applying prediction models on different configurations of the data. There are however limitations of this study to consider.

Firstly, there is, to our knowledge, no accepted definition and classification of intraoperative adverse events in rectal cancer surgery. Different definitions of intraoperative adverse events in surgery in general have been described, however these vary substantially and no consensus on which definition to use has been reached [48]. A recent article prospectively validating a new classification system for intraoperative adverse events was published after the completion of this study [31]. Interestingly it used a definition of intraoperative adverse events similar to the one used in this study [31]. A difference was that they classified the events according to severity, whereas our aim was to investigate the overall occurrence of intraoperative adverse events based on the idea that a problematic surgical procedure of any kind may result in a worse oncological outcome. We tried to create a scientific definition of adverse events, and in order to reduce bias three of the authors independently and systematically reviewed the notes extracted from the surgical documentation within the medical records and, based on the decisions from each reviewer, disagreements were discussed allowing a consensus to be agreed.

Second, the assessment of the occurrence of intraoperative adverse events was based on a retrospective review of the documentation in the medical records. It is possible that there was an underreporting of intraoperative adverse events in the medical records, and there may also be interindividual differences between

TABLE 4 Adverse events, categories

	Total $n = 1208$	Local recurrence $n = 78$	No local recurrence $n = 1130$
Bleeding			
Yes	338 (28%)	37 (47%)	301 (27%)
No	870 (72%)	41 (53%)	829 (73%)
Dissection difficulties			
Yes	139 (12%)	9 (12%)	130 (12%)
No	1069 (88%)	69 (88.5%)	1000 (89%)
Damage to the rectum			
Yes	80 (7%)	12 (15%)	68 (6%)
No	1128 (93%)	66 (85%)	1062 (94%)
Damage to other organs			
Yes	110 (9%)	10 (13%)	100 (9%)
No	1098 (91%)	68 (87%)	1030 (91%)
Problems with division of the bowel			
Yes	78 (6%)	5 (6%)	73 (7%)
No	1130 (94%)	73 (94%)	1057 (94%)
Problems with creation of the anastomosis[a]			
Yes	82 (14%)	1 (5%)	81 (14%)
No	498 (86%)	20 (95%)	478 (86%)
Problems with creation of the stoma[b]			
Yes	20 (2%)	1 (1%)	19 (2%)
No	1057 (98%)	73 (99%)	984 (98%)
Anatomical factors			
Yes	147 (12%)	15 (19%)	132 (12%)
No	1061 (88%)	63 (81%)	998 (88%)
Conversion[c]			
Yes	72 (20%)	8 (36%)	64 (19%)
No	286 (80%)	14 (64%)	272 (81%)
Other			
Yes	65 (5%)	7 (9%)	58 (5%)
No	1143 (95%)	71 (91%)	1072 (95%)

[a]Problems with formation of an anastomosis only analysed for patients where an anastomosis was attempted.

[b]Problems with creation of a stoma only analysed for patients who got a stoma.

[c]Conversion only analysed for patient for whom laparoscopic surgery was attempted.

TABLE 5 Variable importance as the percentage of times selected, and the median and first and third quartiles of the hazard ratio estimates

	Variable importance (%)[a]	Hazard ratio (median, Q1, Q3)[b]
Adverse events		
Yes vs. No ($n = 1208$)	77	3.1 (2.7;3.7)
Radical surgery		
No vs. Yes ($n = 1194$)	99	5.5 (4.4;7)
Tumour stage		
T3-4 vs. T0-2 ($n = 1204$)	97	4.7 (3.7;6.5)
Lymph node metastasis		
Yes vs. No ($n = 1204$)	94	2.4 (2.1;3)
Neoadjuvant treatment		
Yes vs. No ($n = 1208$)	1	0.94 (0.49;1.5)
Type of surgery		
APE vs. AR ($n = 1018$)	63	3.2 (2.8;3.8)
APE vs. HP ($n = 635$)	12	0.55 (0.45;0.63)
AR vs. HP ($n = 763$)	96	0.27 (0.21;0.34)
Rectal washout		
AR Washout vs. no washout ($n = 573$)	57	0.33 (0.25;0.41)
HP Washout vs. no washout ($n = 190$)	74	0.31 (0.23;0.41)

Abbreviations: APE, abdominoperineal excision; AR, anterior resection; HP, Hartmann's procedure.

[a]Percentage of times (out of 1,000 bootstrap samples) that the variable was selected by the LASSO regression.

[b]Maximum likelihood estimates based on data from the samples in which the variable was selected.

surgeons in the extent to which they regarded and reported such events; however, this is unlikely to differ between patients who developed local recurrence and those who did not. Whilst a prospective study could possibly address this issue, this should be done by an independent observer, since the knowledge of the registration of intraoperative adverse events as part of a study could otherwise affect the reporting by the surgeon. In this aspect using the existing documentation in the medical records written by the surgeon directly involved with the surgery, may ensure that there is no systematical bias of the reporting due to the circumstances of a study. Further, since this subject has not been studied in detail previously, we believe that a retrospective study is of value to explore intraoperative adverse events to facilitate future prospective studies.

Finally, as there were few cases of local recurrence during the follow-up period, albeit a large cohort of rectal cancer patients, our study has an insufficient sample size and the limited performance of our model in predicting future recurrence is likely to be partly attributable to this.

In conclusion, in this retrospective population-based study we found intraoperative adverse events to be an independent risk factor for local recurrence after resection of rectal cancer. We suggest that intraoperative adverse events could be an indication for intensive follow-up to detect local recurrences at an earlier stage and

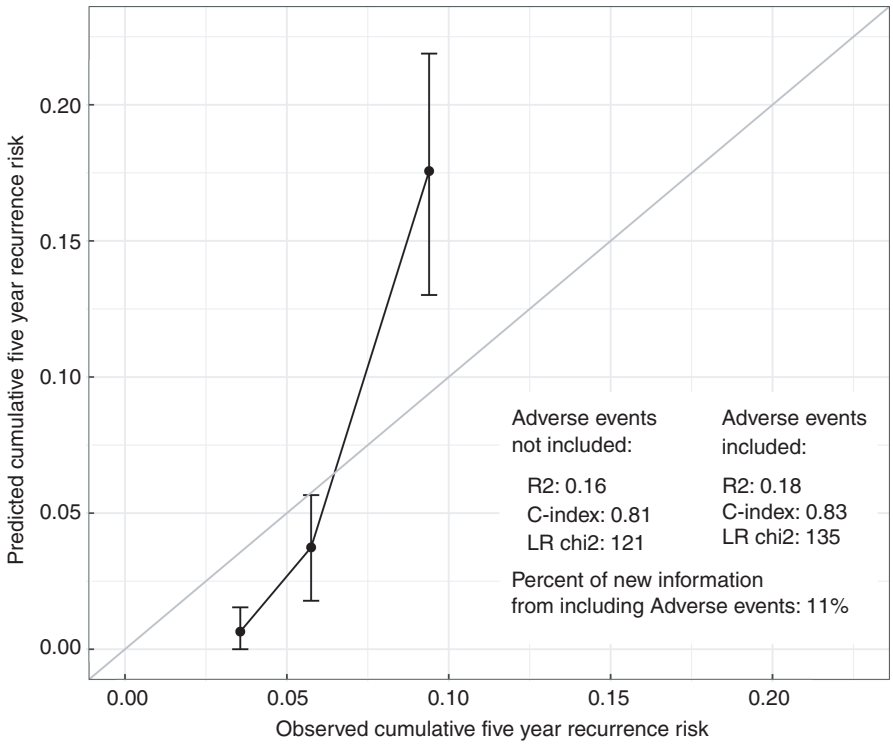

FIGURE 4 Calibration curve displaying the agreement between predicted (vertical axis) and observed (horisontal axis) cumulative 5 year recurrence risk. The 45 degree line indicates perfect calibration

thereby increase the proportion of patients who might benefit from further curative surgery. In order to provide an optimal prediction model studies with larger cohorts are required.

Code for the statistical analyses is available on: https://github.com/dvdsb/Intraoperative-adverse-events-recurrence-rectal-cancer

CONFLICT OF INTEREST

The authors have no conflicts of interest.

AUTHOR CONTRIBUTION

Study conception and design: Waldenstedt, S., Haglind, E., and Angenete, E.; data collection: Waldenstedt, S., and Sjöberg, B.; analysis and interpretation of results: Waldenstedt, S., Bock, D., Haglind, E., and Angenete, E.; draft manuscript preparation: Waldenstedt, S., Bock, D., Haglind E., and Angenete, E. All authors reviewed the results and approved the final version of the manuscript.

ETHICAL APPROVAL

This study was approved by the Ethical Review Board of Gothenburg, Sweden (715–17). The study is registered at Clinical Trials NCT04406974.

DATA AVAILABILITY STATEMENT

Research data are not shared, since this is not included in our ethical approval.

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