Early Closure of a Temporary Ileostomy in Patients With Rectal Cancer

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Early Closure of a Temporary Ileostomy in Patients With Rectal Cancer

A Multicenter Randomized Controlled Trial

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Objective: The objective was to study morbidity and mortality associated with early closure (8–13 days) of a temporary stoma compared with standard procedure (closure after > 12 weeks) after rectal resection for cancer.

Background: A temporary ileostomy may reduce the risk of pelvic sepsis after anastomotic dehiscence. However, the temporary ileostomy is afflicted with complications and requires a second surgical procedure (closure) with its own complications. Early closure of the temporary ileostomy could reduce complications for rectal cancer patients.

Methods: Early closure (8–13 days after stoma creation) of a temporary ileostomy was compared with late closure (>12 weeks) in a multicenter randomized controlled trial, EASY (www.clinicaltrials.gov, NCT01287637) including patients undergoing rectal resection for cancer. Patients with a temporary ileostomy without signs of postoperative complications were randomized to closure at 8 to 13 days or late closure (>12 weeks after index surgery). Clinical data were collected up to 12 months. Complications were registered according to the Clavien-Dindo Classification of Surgical Complications, and Comprehensive Complication Index was calculated.

Results: The trial included 127 patients in eight Danish and Swedish surgical departments, and 112 patients were available for analysis. The mean number of complications after index surgery up to 12 months follow-up was significantly lower in the intervention group (1.2) compared with the control group (2.9), P < 0.0001.

Conclusions: It is safe to close a temporary ileostomy 8 to 13 days after rectal resection and anastomosis for rectal cancer in selected patients without clinical or radiological signs of anastomotic leakage.

Keywords: Clavien-Dindo classification, early closure, ileostomy, morbidity, mortality, randomized controlled trial

Patients with low rectal cancer often receive a temporary ileostomy at the time of resection of the rectum to reduce the risk of symptomatic anastomotic dehiscence. The temporary ileostomy was introduced to decrease the clinical consequences of an anastomotic leak but it has not been shown to reduce the risk of anastomotic leakage as such. However, studies have shown complication rates up to 43% related to the temporary ileostomy, including readmissions, dehydration, and chronic renal failure. Most patients with a temporary ileostomy will keep their stoma at least 3 months, and it is not unusual that the stoma is left in place much longer, and for a few patients it becomes permanent.

Closure of the temporary ileostomy is associated with a low mortality, but the morbidity may be more than 20%. Timing of stoma closure has previously been investigated in a few prospective studies that mainly focused on morbidity and mortality related to early closure of the stoma. These studies did not demonstrate any significant effect on morbidity or mortality related to early closure. In other studies investigating the possibility of an earlier closure, the results have been promising.

The aim of this trial was to explore if morbidity and mortality was reduced within 12 months after rectal resection in patients treated for low rectal cancer, and if the stoma was closed early (8–13 days after stoma creation) compared with late closure of the temporary ileostomy (a minimum of 12 weeks after stoma creation).

The primary endpoint was the mean number of complications after index operation and up to 12 months. Two secondary endpoints were (i) the proportion of patients with at least one complication with Clavien-Dindo Classification of Surgical Complications (Clavien-Dindo classification) severity grade IIa, IIb, IIIa, or IIIb after index surgery and up to 12 months and (ii) the mean number of stoma-related complications after index surgery and up to 12 months. Supporting endpoints were the Comprehensive Complication Index (CCI) after index surgery and up to 12 months and creatinine levels.

METHODS

Design The trial was designed as a randomized controlled multicenter trial comparing early with late closure of temporary ileostomy in eight Danish and Swedish surgical departments. Screening for and inclusion of participants was made after the index surgery (total mesorectal excision (TME) for rectal cancer) with creation of a temporary ileostomy. Follow-up of patients was at the time of
closure, and 3, 6, and 12 months after index surgery. 

The study protocol specified 72 evaluable patients per group to have 80% power to detect a 66% reduction in the risk of complications. Because of slow enrollment, fewer evaluable patients were reached and before data analysis a re-calculation was performed. With 60 evaluable patients per group we would have 80% power to detect a 62.5% reduction in the annual mean number of complications using a 2-sided test with 5% significance level and assuming a mean complication rate of 0.45 in the control group.

### Sample Size

The study protocol specified 72 evaluable patients per group to have 80% power to detect a 66% reduction in the risk of complications. Because of slow enrollment, fewer evaluable patients were reached and before data analysis a re-calculation was performed. With 60 evaluable patients per group we would have 80% power to detect a 62.5% reduction in the annual mean number of complications using a 2-sided test with 5% significance level and assuming a mean complication rate of 0.45 in the control group.

### Statistical Methods

A detailed statistical analysis plan was made before data analysis. Analyses were made on all randomized patients using an intention to treat perspective (ITT). All primary and secondary endpoints were analyzed with a generalized linear model with a log-link function with group (early vs late reversal) and hospital as factors. For the primary endpoint a negative binomial distribution was used. Results were to be presented as geometric mean ratio, 95% confidence intervals (CI) and a P-value for the test of a null hypothesis of no difference in average number of complications up to 12 months post index-surgery. For the first secondary endpoint a binomial distribution was used with robust variance estimation using Generalized Estimating Equations. Results are presented as risk ratio and 95% CI. For the second secondary endpoint a negative binomial distribution was used. The familywise error rate was controlled in the strong sense by a fixed sequence Bonferroni procedure where the two secondary hypotheses were only tested at 2.5% level if the primary hypothesis was rejected at the 5% level. Sensitivity adjusted analyses were performed with sex, age, body mass index (BMI), comorbidity, and radiotherapy as covariates.

### Ethics and Informed Consent

The project was approved by the Science Ethical Committee for the Capital Region in Denmark (Protocol ID: H-1–2010–113) and in Sweden the project was approved by the Ethical Approval Committee in Göteborg (Dnr 064–2011). Before inclusion patients were informed about the study and all participating patients returned a signed consent form.

### Approval of Data Security

The project was approved by the Data Protection Agency in Denmark, and by the Personal Data Representative at the Sahlgrenska University Hospital, Göteborg, Sweden.

### Trial Registration

The project was registered at www.clinicaltrials.gov (identifier: NCT01287637) before patient inclusion.

## RESULTS

Overall Results

We assessed 418 patients for eligibility, and 291 of these did not meet the inclusion criteria because of suspected anastomotic leakage (n = 53), unwillingness to participate (n = 53), other medical reasons (n = 159), and where inclusion was missed (n = 42) (Fig. 1). Hence, 127 patients were randomized and out of these another
15 patients were excluded. In summary, 112 patients were included from February 2011 and with last follow-up of the last patient in November 2015. There were 55 patients in the early- and 57 patients in the late closure group available for analysis, respectively (Fig. 1).

There were no violations of the randomization.

Baseline demographic data are shown in Table 1. The intervention group included a larger proportion of females compared with the control group (Table 1). In all other respects the groups were comparable. Perioperative details of loop ileostomy closure and its postoperative complications were comparable between groups (Tables 2 and 3).

Median time from index surgery to closure was 11 days in the early group and 148 days in the late group (Table 2). At 3, 6, and 12-months follow up after index surgery there were more

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**FIGURE 1.** Participant flow diagram.
complications in the control group (Table 3). Two patients in the control group underwent earlier closure because of high-volume stomal output and stomal retraction, respectively. These events were regarded as complications classified as Clavien-Dindo Grade IIIb (Table 3). One patient in the intervention group suffered from severe renal failure because of high volume output at the 3 months follow up (classified Clavien-Dindo Grade IVa). This patient had undergone a failed attempt to closure within 13 days of index surgery, which lead to prolonged duration of the loop ileostomy. The attempted surgery was considered a postoperative complication, and the patient remained in the early closure group on an intention to treat basis.

Primary endpoint: The mean number of complications after index surgery up to the 12 months follow up was significantly lower in the intervention group (mean number of complications was 1.24 in the intervention group compared with 2.88 in the control group) with a ratio for intervention versus control of 0.42 (95% CI 0.32–0.57), \( P < 0.0001 \) (Tables 2 and 3). The adjusted analysis showed similar results.

Secondary Endpoints

When comparing more severe complications (Clavien-Dindo Grade IIIa or higher), there was no significant difference between the two groups (proportion of patients with at least one complication Clavien-Dindo Grade IIIa or higher was 0.22 for the intervention group and 0.29 for the control group, \( P = 0.32 \)). The results were similar in the adjusted analysis.

The mean number of stoma related complications was significantly higher in the control group (intervention group 0.30 and control group 1.25) with a ratio for intervention versus control of 0.25 (95% CI 0.15–0.42), \( P < 0.0001 \) (Table 4). The adjusted analysis showed similar results.

Supporting Endpoints

When comparing more severe complications (Clavien-Dindo Grade IIIa or higher), there was no significant difference between the two groups (proportion of patients with at least one complication Clavien-Dindo Grade IIIa or higher was 0.22 for the intervention group and 0.29 for the control group, \( P = 0.32 \)). The results were similar in the adjusted analysis.

The mean number of stoma related complications was significantly higher in the control group (intervention group 0.30 and control group 1.25) with a ratio for intervention versus control of 0.25 (95% CI 0.15–0.42), \( P < 0.0001 \) (Table 4). The adjusted analysis showed similar results.

DISCUSSION

This clinical trial provides evidence of the safety, efficacy, and feasibility of early closure of a temporary ileostomy in selected
patients with rectal cancer with a follow up of 12 months after index operation. Only patients assessed for clinically relevant complications related to the index surgery and who were found appropriately fit were invited to enter the trial. Therefore, only patients not showing clinical or radiological signs of adverse events after the rectal cancer operation were included and randomized.

We found a significant difference between the two groups regarding our primary endpoint, which was the mean number of complications within 12 months of index surgery. Further, patients in the intervention group had fewer complications than patients in the control group during the follow up. There was no significant difference in the rate of severe complications, grade IIIa, and above according to the Clavien-Dindo classification. The pattern of severe complications varied between intervention and control groups during the follow-up period (Table 3) and in particular there seemed to be more severe complications in the control group between 6 and 12 months compared with the intervention group. The total number of complications differed significantly over time between groups. In the study by Alves et al, patients had an overall morbidity of 31% in the early closure group and 38% in the late closure group at 90 days after stoma creation, which was similar to our results. However, they did not report overall complications later in the follow-up period.

Patients included in this trial were comparable with regard to baseline characteristics apart from more female participants in the intervention group. The adjusted analysis showed similar results with no impact of sex, age, BMI, comorbidity, or neoadjuvant radiotherapy.

Data on surgical closure of the loop ileostomy did not differ between the groups, although 3 patients in the intervention group and 4 patients in the control group experienced complications and some of them had more than one complication. Our results indicated that early closure of a temporary ileostomy is safe, as has been suggested before. The rate of overall complications reported from other studies was higher and one possible explanation could be criteria for inclusion and exclusion in our trial.

We found a significant difference in the mean number of stoma related complications, in particular relieving patients in the

### Table 2. Details of Loop Ileostomy Closure

<table>
<thead>
<tr>
<th>Randomization Group</th>
<th>Early Closure (n = 55)</th>
<th>Late Closure (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time with ileostomy (days)</td>
<td>11 (8–152)</td>
<td>148 (64–665)</td>
</tr>
<tr>
<td>Bleeding (mL)</td>
<td>5 (0–200)</td>
<td>5 (0–700)</td>
</tr>
<tr>
<td>Time duration of surgery (min)</td>
<td>50 (17–180)</td>
<td>71 (31–401)</td>
</tr>
<tr>
<td>Anastomosis (ileo-ileo anastomosis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handsewn</td>
<td>45 (82%)</td>
<td>40 (70%)</td>
</tr>
<tr>
<td>Stapled</td>
<td>10 (18%)</td>
<td>15 (26%)</td>
</tr>
<tr>
<td>Epidural anaesthesia</td>
<td>1 (2%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Time until passing of gas (days)</td>
<td>1 (0–6)</td>
<td>2 (0–8)</td>
</tr>
<tr>
<td>Time until fully oral nutrition (days)</td>
<td>1 (0–23)</td>
<td>2 (0–20)</td>
</tr>
<tr>
<td>Time in intensive care unit (days)</td>
<td>0 (0–0)</td>
<td>0 (0–0)</td>
</tr>
<tr>
<td>Hospital stay after closure (days)</td>
<td>4 (2–27)</td>
<td>4 (2–28)</td>
</tr>
<tr>
<td>Postoperative complication (number of patients)</td>
<td>4 (7%)</td>
<td>4 (7%)</td>
</tr>
</tbody>
</table>

Classification according to Clavien-Dindo (number of complications)

- Grade I: 1
- Grade II: 3
- Grade IIIa: 0
- Grade IIIb: 2
- Grade IVa: 0
- Grade IVb: 0
- Grade V: 0

Type of complication

- Infection: 2
- Fistula/anastomotic leakage: 0
- Bleeding: 0
- Nausea/vomiting: 1
- Cardiopulmonary: 0
- Liver insufficiency: 0
- Pain: 1
- Allergy: 0
- Pancreatitis: 0
- Other (specification): 2

Cause of reoperation – after loop ileostomy closure

- Failed attempt of stoma closure: 1
- Small bowel obstruction: 1

Numbers are in median. Percentages or range is given in parenthesis.

1 Patient did not go through closure due to metastatic disease.

2 Patients underwent closure more than 365 days after index surgery (440 and 665 days, both in the control group). Data were registered retrospectively that enabled identifying information regarding closure later than the follow-up period. Data on stoma related complications were only registered within the follow-up period of 12 months.

§Missing data in 1 patient.

*Small bowel obstruction (n = 1), failed attempt of stoma closure because of swelling of small bowel (n = 1).
TABLE 3. Details of Complications Registered at Follow-up 3, 6, and 12 Months After Index Operation and Including Complications Occurring From Leaving Hospital Until 3 Months, From 3 to 6 Months and From 6 to 12 Months, Respectively

<table>
<thead>
<tr>
<th>Classification According to Clavien-Dindo (^{12,13}) (Number of Complications)</th>
<th>Randomization Group</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postoperative complication (number of patients)</td>
<td>Early Closure (n = 55)</td>
<td>Late Closure (n = 57)</td>
<td>Early Closure (n = 55)</td>
<td>Late Closure (n = 57)</td>
</tr>
<tr>
<td>Grade I</td>
<td>7</td>
<td>11</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Grade II</td>
<td>4</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>5</td>
<td>9</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade V</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reoperations within 12 months - causes</td>
<td>Early Closure (n = 55)</td>
<td>Late Closure (n = 57)</td>
<td>Early Closure (n = 55)</td>
<td>Late Closure (n = 57)</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Presacral abscess (leakage of the colo-anal anastomosis)</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abscess</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bleeding peptic ulcer</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stenosis in colo-anal anastomosis</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TABLE 4. Details of Complications Related to the Loop Ileostomy From Index Surgery Until Closure of the Stoma

<table>
<thead>
<tr>
<th>Classification According to Clavien-Dindo (^{12,13}) (Number of Complications)</th>
<th>Randomization Group</th>
<th>Early Closure (n = 55)</th>
<th>Late Closure (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stoma related complications</td>
<td>Early Closure (n = 55)</td>
<td>Late Closure (n = 57)</td>
<td>Early Closure (n = 55)</td>
</tr>
<tr>
<td>Number of patients</td>
<td>13/55 (24%)</td>
<td>44/57 (77%)</td>
<td>13/55 (24%)</td>
</tr>
<tr>
<td>Grade I</td>
<td>13</td>
<td>63</td>
<td>3</td>
</tr>
<tr>
<td>Grade II</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Grade IIIa</td>
<td>2</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Grade IIIb</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade IVa</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Grade IVb</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade V</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Type of stoma related complications</td>
<td>Early Closure (n = 55)</td>
<td>Late Closure (n = 57)</td>
<td>Early Closure (n = 55)</td>
</tr>
<tr>
<td>Skin irritation</td>
<td>3</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Stomal ulcer</td>
<td>3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Parastomal infection</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Leakage outside appliance bag</td>
<td>3</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>High volume output</td>
<td>5</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Parastomal hernia</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stenosis</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Prolaps</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retraction</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{1}\) Renal failure because of high volume output. This patient underwent a failed attempt to closure within 13 days after index surgery, which lead to delayed loop ileostomy closure. 
\(^{2}\) (i) Stomal retraction (n = 1), which lead to earlier closure, (ii) symptomatic parastomal hernia (n = 1), which was sutured at closure, and (iii) high volume output (n = 1), which lead to earlier closure of the loop ileostomy.
intervention group from skin irritation, ulcerations, and problems with leakage and of high-volume output. Although stoma related complications may seem less severe than complications > IIIa in the Clavien-Dindo classification, these complications can be tiresome, distressing, and embarrassing for the patient.21,22 The observed difference in median CCI of 15.7 units pointed to a clinically relevant advantage for the intervention group.14

Many patients have their loop ileostomy considerably longer than the suggested 12 weeks, which also could be seen in our study where median time until closure in the control group was 148 days (equivalent to 5 months). Other studies have pointed out that 20% of the temporary ileostomies were never closed,23 but only 3 patients (3%) in our trial did not undergo closure within the follow-up period of 12 months after index surgery. Of those, two patients did eventually undergo reversal of the loop ileostomy, although later than 12 months after index surgery, and the third patient who deceased from metastatic disease within 12 months was regarded as a permanent loop ileostomy carrier. Previous reports have suggested reasons for nonclosure as old age, surgical complications, and comorbidity.3 Possible explanations for the high closure rate <12 months in our trial most likely include focus on closure of the ileostomy in the trial setting.

In accordance with the report by Gessler et al,15 we found that a temporary ileostomy has a negative effect on renal function, reflecting that for a few individuals a loop ileostomy may have a systemic effect as well. Strengths of this trial include the randomized design, the screening log at the including hospitals enabling an evaluation of external validity and the thorough examination of patients after inclusion and before randomization to ascertain that patients did not have a subclinical anastomotic leakage.

It could be considered a limitation that not all patients screened for participation were included because of the strict inclusion criteria. We screened 418 patients in the participating centers and only 127 patients were included and randomized and finally 112 patients were included in the analysis (Fig. 1). However, this was a safety measure and even if only 30% of the entire group can undergo early closure this represents significant improvements for the patients. The screening-logs were complete and all non-included patients were registered with specific reasons for the non-inclusion. Another limitation was the coding of complications as it was not possible to blind the surgeon or the research nurse who included patients were registered with specific reasons for the non-inclusion. Another limitation was the coding of complications as it was not possible to blind the surgeon or the research nurse who carried out the actual coding of the complications, which may have led to observer bias.

CONCLUSIONS

We found that in selected patients without clinical, radiological, or endoscopic signs of a leakage early closure of the temporary ileostomy after surgery for rectal cancer resulted in a significantly lower mean number of complications compared with late closure. We also found low numbers of severe complications in both groups suggesting that patients should be considered for early closure of an ileostomy if they have no signs of anastomotic leakage in the postoperative period after rectal resection.

ACKNOWLEDGMENTS

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