Quality of life in a randomized trial of early closure of temporary ileostomy after rectal resection for cancer (EASY trial)

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Background: A temporary ileostomy may reduce symptoms from anastomotic leakage after rectal cancer resection. Earlier results of the EASY trial showed that early closure of the temporary ileostomy was associated with significantly fewer postoperative complications. The aim of the present study was to compare health-related quality of life (HRQOL) following early versus late closure of a temporary ileostomy.

Methods: Early closure of a temporary ileostomy (at 8–13 days) was compared with late closure (at more than 12 weeks) in a multicentre RCT (EASY) that included patients who underwent rectal resection for cancer. Inclusion of participants was made after index surgery. Exclusion criteria were signs of anastomotic leakage, diabetes mellitus, steroid treatment, and signs of postoperative complications at clinical evaluation 1–4 days after rectal resection. HRQOL was evaluated at 3, 6 and 12 months after resection using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30 and QLQ-CR29 and Short Form 36 (SF-36®).

Results: There were 112 patients available for analysis. Response rates of the questionnaires were 82–95 per cent, except for EORTC QLQ-C30 at 12 months, to which only 54–55 per cent of the patients responded owing to an error in questionnaire distribution. There were no clinically significant differences in any questionnaire scores between the groups at 3, 6 or 12 months.

Conclusion: Although the randomized study found that early closure of the temporary ileostomy was associated with significantly fewer complications, this clinical advantage had no effect on the patients’ HRQOL. Registration number: NCT01287637 (https://www.clinicaltrials.gov).

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Introduction

Low anterior resection with total mesorectal excision is regarded as one of the optimal surgical treatments for potentially curable carcinoma of the rectum1,2. Because of the low anastomosis close to the pelvic floor, patients often receive a temporary ileostomy at the time of the resection to reduce the risk of symptomatic anastomotic dehiscence3 and its clinical consequences4–6. However, studies7–9 have reported considerable morbidity related to the temporary ileostomy, with complication rates of up to 50 per cent. Most patients with a temporary ileostomy have the stoma for at least 3 months, and it is not unusual for it to be left in place much longer. For some patients the stoma becomes permanent10.

Data regarding quality of life (QOL) in patients receiving a diverting stoma as part of their rectal cancer treatment are limited11–14. In prospective studies it has been suggested that patients with a stoma may suffer from impaired health-related quality of life (HRQOL)15, which may improve at stoma closure2. Complications such as stoma leakage, parastomal skin irritation, dietary restrictions, retraction and prolapse of the stoma have been reported to have significant impact on the patient’s daily life12.

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The aim of the present study was to compare HRQOL at 3, 6 and 12 months after rectal resection for cancer in a multicentre RCT comparing early versus late closure of a temporary ileostomy (EASY trial).16,17

Methods
The EASY trial was designed as a randomized multicentre trial16 comparing early with late closure of a temporary ileostomy regarding risk of complications. Screening for and inclusion of participants was made after index surgery (total mesorectal excision for rectal cancer including creation of a temporary ileostomy). Exclusion criteria were diabetes mellitus, ongoing steroid treatment, signs of postoperative complications at clinical evaluation 1–4 days after rectal resection and inability to understand the Danish or Swedish language. Patients with no adverse signs were invited to participate and, after informed consent, underwent further investigation with contrast-enhanced CT or a flexible endoscopy of the rectum, or both, performed 6–8 days after stoma creation to ensure that no patient with signs of anastomotic leakage was included. Patients were randomized to either the intervention group with early closure (day 8–13 after stoma creation) or the control group with late closure (more than 12 weeks after stoma creation) of the ileostomy.

The primary endpoint of the study was the mean number of complications after rectal resection and up to 12 months; these results have been published previously17. The present paper reports the secondary endpoints, HRQOL and QOL, at 3, 6 and 12 months after the index operation.

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

The protocol was registered at https://www.clinicaltrials.gov (NCT01287637) before patient inclusion.

Patients
Eight hospitals in Denmark and Sweden participated in the study, but three centres (with a total of 8 patients) were excluded as they failed to maintain a screening log. Consenting patients were asked to complete questionnaires at 3, 6 and 12 months after stoma creation (rectal resection). The questionnaires included the 36-item Short Form 36 (SF-36®; Rand Corporation, Santa Monica, California, USA) and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) CR29 and C30. Data regarding demographic details, tumour stage and height, chemoradiotherapy and all complications within 12 months of surgery were registered in case report forms.

Randomization
Consenting patients who fulfilled the inclusion criteria were randomized either to the intervention group with early closure of the ileostomy or to the control group with late closure. Randomization was executed in computer-generated blocks of six. The randomization was performed on the surgical ward using sequentially numbered thick, opaque and sealed envelopes. Blinding of the intervention was not possible.

Health-related quality-of-life instruments
Short Form 36
SF-36® is a generic tool that evaluates patients’ self-reported quality of life.18,19 It consists of 36 items that measure eight dimensions of health on a multi-item scale, including social and physical function. The scoring scale ranges from 0 to 100, with lower scores indicating worse health. The instrument has been validated, and for comparison in this study a Swedish reference population was used.20

EORTC QLQ-C30 and QLQ-CR29
The EORTC QLQ-C30 is a questionnaire developed to assess QOL in patients with cancer, and consists of five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea, and vomiting), one global health status and QOL scale, and six single-item measures (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties).21 A high score on the functional scale represents a high level of functioning, whereas a high score on the symptom scale represents a high level of symptoms.

The EORTC QLQ-CR29 was designed for use in patients undergoing treatment for colorectal cancer. It was derived from the EORTC QLQ-C38 questionnaire, as there was a need for an update in the colorectal module.22 The questions assess disease symptoms, side-effects of treatment, body image, future perspective, and sexual function and interest. Both questionnaires have been validated internationally and were available in Danish and Swedish versions.22,23
All questionnaires were administered at 3, 6 and 12 months after stoma creation.

**Statistical analysis**

The study was part of a RCT with power calculated for the primary endpoint. Group sizes in the EASY trial were set to 72 patients per group to evaluate complication rates\textsuperscript{16,17}. In Krouse \textit{et al.}\textsuperscript{24} a minimally important difference of 8 units was used for the different scales of SF-36®. Physical and mental component scores had a standard deviation (s.d.) of up to 15 units, and the eight specific scales had s.d. values in the range 17–33. With group sizes of 72 or 55 and a s.d. of 17 or 15 respectively, there will be 80 per cent power to detect a true difference of 8 units.

The questionnaires SF-36®\textsuperscript{25}, EORTC QLQ-C30\textsuperscript{26} and QLQ-CR29\textsuperscript{23} were scored according to the methods recommended by the developers; missing data were handled as instructed in the scoring manuals. Before analysis, based on the literature and previous data, the authors chose to present the functional scales and global health status/QOL of the EORTC QLQ-C30 questionnaire, and the functional scales (urinary frequency, stool frequency and body image) of the EORTC QLQ-CR29 questionnaire. At 12-month follow-up, several patients (20...
Table 1 Baseline and preoperative characteristics of patients randomized to early or late closure

| Characteristic                              | Early closure (n = 55) | Late closure (n = 57) |
|---------------------------------------------|------------------------|-----------------------|
| Age (years)*                                | 67 (36–82)             | 67 (39–81)            |
| Sex ratio (F : M)                           | 31 : 24                | 21 : 36               |
| BMI (kg/m²)*                                | 24 (17–32)             | 23 (19–35)            |
| Co-morbidity                                |                        |                       |
| Ischaemic heart disease                     | 5                      | 8                     |
| Hypertension                                | 17                     | 13                    |
| COPD                                        | 2                      | 2                     |
| Renal disease                               | 0                      | 0                     |
| Other                                       | 9†                     | 4§                    |
| Radiotherapy                                | 16 (29)                | 16 (28)               |
| Long-term                                   | 5 (9)                  | 5 (9)                 |
| Adjuvant chemotherapy                       | 22 (40)                | 23 (40)               |
| Marital status                              |                        |                       |
| Single                                      | 5 (9)                  | 9 (16)                |
| Married                                     | 42 (76)                | 43 (75)               |
| Widowed                                     | 8 (15)                 | 5 (9)                 |
| Higher education                            | 34 (62)                | 37 (65)               |
| Employed                                    |                        |                       |
| Yes                                         | 25 (45)                | 25 (44)               |
| No                                          | 29 (53)††              | 32 (56)               |
| Smoker                                      | 6 (11)                 | 4 (7)                 |
| No. of pack years*                          | 30 (16–30)††           | 26 (20–50)††          |
| Alcohol intake > 60 g/day                   | 0 (0)                  | 0 (0)                 |
| Lower border of tumour (cm from anal verge) |                        |                       |
| 5–9                                        | 27 (49)                | 24 (42)               |
| 10–15                                       | 27 (49)                | 33 (58)               |
| > 15                                       | 1 (2)                  | 0 (0)                 |
| UICC clinical stage**                       |                        |                       |
| I                                           | 12 (22)                | 19 (33)               |
| II                                          | 21 (38)                | 13 (23)               |
| III                                         | 18 (33)                | 20 (35)               |
| IV                                          | 3 (5)                  | 1 (2)                 |
| Method of evaluation of anastomosis before ileostomy closure | | |
| CT                                          | 14 (25)                | 19 (33)               |
| Rectoscopy                                  | 14 (25)                | 10 (18)               |
| CT + rectoscopy                             | 27 (49)                | 28 (49)               |
| Total length of hospital stay (days) *      | 14 (11–42)             | 14 (7–44)             |

Values in parentheses are percentages unless indicated otherwise; *values are median (range). †Data missing for two patients. ‡Asthma (2), depression (1), idiopathic thrombocytopenic purpura (1), lymphoma (1), Waldenström’s macroglobulinaemia (1), osteoporosis (1), Sjögren syndrome (1), thyrotoxicosis (1). §Depression (1), hyperlipidaemia (1), hypothyroidism (1), meningioblastoma (1). ¶Data missing for one patient. #Data missing for three patients. **Data missing for one patient in each group; in addition, three patients in the late closure group had T0 N0 M0 disease and were therefore not classified. ††For both index surgery and loop ileostomy closure. COPD, chronic obstructive pulmonary disease; UICC, International Union Against Cancer. Table reproduced with permission from Wolters Kluwer Health Inc. Danielsen AK, Park J, Jansen JE, Bock D, Skullman S, Wedin A et al. Early closure of a temporary ileostomy in patients with rectal cancer: a multicenter randomized controlled trial. Ann Surg 2017; 265 (2): 284–290. https://journals.lww.com/annalsofsurgery/.

in the intervention group and 16 in the control group) were, by mistake, given an incomplete questionnaire in which questions 16–30 of the EORTC QLQ-C30 were missing. Before analysis, the decision was made to include physical and role functioning, as these functional scales are scored using questions 1–15 in accordance with the EORTC manual. No other scales or items were analysed for these patients in the EORTC QLQ-C30 at 12-month follow-up. However, EORTC QLQ-CR29 and SF-36® were analysed at 12-month follow-up. As the distribution of the incomplete questionnaires was independent of the observable characteristics of the patients who received them, interpreting the missing data as being completely random is reasonable and imputation was considered unnecessary.

Owing to the characteristics of the data, the different scales of SF-36® and EORTC were summarized by median (i.q.r.) values, and group comparisons were made using the Wilcoxon rank sum test and the two-sample Hodges–Lehmann estimator.

SF-36® scores were compared with those in a general Swedish reference population. For each of the
Table 2  SF-36® scores at 3, 6 and 12 months after rectal resection

|                      | 3 months                      | 6 months                      | 12 months                     |
|----------------------|-------------------------------|-------------------------------|-------------------------------|
|                      | Median (i.q.r.)               | H–L*                          | P†                            |
| Physical functioning |                               |                               |                               |
| Early                | 90 (75–95)                    | 0 (–5, 5)                     | 0.64                          |
| Late                 | 90 (80–95)                    |                               |                               |
| Role physical        |                               |                               |                               |
| Early                | 75 (50–96–9)                  | 12.5 (0, 18–8)                | 0.025                         |
| Late                 | 62.5 (43–87–75)               |                               |                               |
| Bodily pain          |                               |                               |                               |
| Early                | 80 (52–100)                   | 0 (–10, 0)                    | 0.858                         |
| Late                 | 74 (62–100)                   |                               |                               |
| General health       |                               |                               |                               |
| Early                | 71.6 (52–88–5)                | –5 (–15, 2)                   | 0.139                         |
| Late                 | 77 (67–87)                    |                               |                               |
| Vitality             |                               |                               |                               |
| Early                | 62.5 (43–81–3)                | 4.2 (–6, 12.5)                | 0.441                         |
| Late                 | 68.8 (56–81–3)                |                               |                               |
| Social functioning   |                               |                               |                               |
| Early                | 75 (62–100)                   | 0 (–12.5, 0)                  | 0.468                         |
| Late                 | 87.5 (75–100)                 |                               |                               |
| Role emotional       |                               |                               |                               |
| Early                | 83.3 (58–100)                 | 0 (0, 8.3)                    | 0.345                         |
| Late                 | 83.3 (50–100)                 |                               |                               |
| Mental health        |                               |                               |                               |
| Early                | 80 (55–90)                    | 5 (–5, 10)                    | 0.217                         |
| Late                 | 85 (65–90)                    |                               |                               |
| Mental component score |                               |                               |                               |
| Early                | 52.5 (40–58)                  | 1 (–2.6, 5)                   | 0.588                         |
| Late                 | 53 (44–57)                    |                               |                               |
| Physical component score |                       |                               |                               |
| Early                | 51.8 (40–58)                  | –0.5 (3.8, 3.4)               | 0.823                         |
| Late                 | 51.2 (46–54)                  |                               |                               |

*Two-sample Hodges-Lehmann (H–L) estimator with 95 per cent asymptotic confidence limits in parentheses. SF-36®, Short Form 36. †Wilcoxon rank sum test for difference between early and late closure.

eight scales, the individual levels were compared with age-matched (17–34, 35–49, 50–64, and 65 or more years) mean levels from the reference population. The proportion of patients with values below the reference levels was compared between the intervention and control group using a χ² test. The software packages SPSS® version 23 (IBM, Armonk, New York, USA), SAS® version 9.4 (SAS Institute, Cary, North Carolina, USA) and R version 3.2.37 were used for statistical analysis. Scores for SF-36®, EORTC QLQ-C30 and QLQ-CR29 were derived and summarized by median (i.q.r. values).

Results

The EASY trial assessed 418 patients for eligibility. After exclusion of 291 patients, 127 patients were randomized (Fig. 1). A further 15 patients were excluded, eight from three centres that were excluded from the study as they failed to maintain a screening log. In summary, 112 patients were included from February 2011, with the last follow-up in November 2015. Some 55 patients in the intervention (early closure) group and 57 in the control (late closure) group were available for analysis. There were no violations of the randomization. Except for a larger proportion of women in the intervention group, baseline demographic characteristics and clinical data were similar in the two groups (Table 1).

Questionnaire response rates were generally around 90 (range 82–95) per cent, excluding the EORTC QLQ-C30 at 12-month follow-up, owing to missing questions as described in the Methods section (Fig. 1).

SF-36® scores were similar between the two groups, with no differences in the physical component score or the mental component score, but significant differences in role physical, bodily pain and mental health at 3, 12 and 12 months respectively (Table 2). All dimensions in SF-36® improved over time. At 3 months, a majority of patients in both groups scored values below mean levels in the reference population20, especially regarding role physical. At 12 months, 52–85 per cent of the patients scored higher
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Table 3  EORTC QLQ-C30 scores at 3, 6 and 12 months after rectal resection

|                  | 3 months          | 6 months          | 12 months         |
|------------------|-------------------|-------------------|-------------------|
|                  | Median (i.q.r.)   | H–L*              | P†                | Median (i.q.r.)   | H–L*              | P†                | Median (i.q.r.)   | H–L*              | P†                |
| Global quality of life |                  |                   |                   |                  |                   |                   |                  |                   |                   |
| Early             | 75 (50–83.3)      | 0 (–8.3, 8.3)     | 0.941             | 66.7 (60–83.3)   | 0 (–8.3, 8.3)     | 0.961             | 83.3 (50–91.7)   | 0 (–16.7, 8.3)   | 0.889             |
| Late              | 66.7 (58.3–83.3)  |                   |                   | 66.7 (66.7–83.3) |                   |                   | 83.3 (66.7–91.7) |                   |                   |
| Physical functioning |                  |                   |                   |                  |                   |                   |                  |                   |                   |
| Early             | 93.3 (73.3–100)  | 0 (0, 6.7)        | 0.634             | 93.3 (80–100)    | 0 (–6.7, 0)       | 0.433             | 93.3 (73.3–100) | 0 (–13.3, 0)     | 0.137             |
| Late              | 93.3 (73.3–100)  |                   |                   | 93.3 (80–100)    |                   |                   | 100 (80–100)     |                   |                   |
| Role functioning  | 83.3 (66.7–100)  | –16.7 (–16.7, 0)  | 0.066             | 100 (66.7–100)   | 0 (0, 0)          | 0.503             | 100 (66.7–100)  | 0 (0, 0)          | 0.793             |
| Emotional function| 83.3 (66.7–100)  | 8.3 (0, 16.7)     | 0.023             | 83.3 (66.7–100)  | –8.3 (–16.7, 0)   | 0.031             | 91.7 (66.7–100) | 0 (–8.3, 0)      | 0.409             |
| Cognitive function| 91.7 (83.3–100)  |                   |                   | 91.7 (75–100)    |                   |                   | 91.7 (66.7–100) |                   |                   |
| Social functioning| 100 (83.3–100)   | 0 (0, 0)          | 0.447             | 83.3 (83.3–100)  | 0 (–16.7, 0)      | 0.131             | 100 (83.3–100)  | 0 (0, 0)          | 0.652             |
|                  | 83.3 (66.7–100)  | 0 (0, 0)          | 0.583             | 83.3 (66.7–100)  | 0 (0, 0)          | 0.882             | 83.3 (66.7–100) | 0 (–16.7, 0)     | 0.142             |

*Two-sample Hodges–Lehmann (H–L) estimator with 95 per cent asymptotic confidence limits in parentheses. EORTC, European Organisation for Research and Treatment of Cancer. †Wilcoxon rank sum test for difference between early and late.

Table 4  EORTC QLQ-CR29 scores for selected functions at 3, 6 and 12 months after rectal resection

|                  | 3 months          | 6 months          | 12 months         |
|------------------|-------------------|-------------------|-------------------|
|                  | Median (i.q.r.)   | H–L*              | P†                | Median (i.q.r.)   | H–L*              | P†                | Median (i.q.r.)   | H–L*              | P†                |
| Urinary frequency |                  |                   |                   |                  |                   |                   |                  |                   |                   |
| Early             | 16.7 (0–33.3)    | 0 (0, 16.7)       | 0.323             | 16.7 (0–50)      | 0 (–16.7, 0)      | 0.353             | 16.7 (0–33.3)    | 0 (0, 16.7)       | 0.268             |
| Late              | 16.7 (0–50)      |                   |                   | 16.7 (8–41.7)    |                   |                   | 33.3 (30–50)     |                   |                   |
| Stool frequency   |                  |                   |                   |                  |                   |                   |                  |                   |                   |
| Early             | 33.3 (16.7–50)   | 0 (0–16.7)        | < 0.001           | 33.3 (16.7–50)   | 0 (0–33.3)        | 0.068             | 33.3 (16.7–50)   | 0 (0, 16.7)       | 0.611             |
| Late              | 33.3 (16.7–33.3) |                   |                   | 16.7 (0–66.7)    |                   |                   | 33.3 (16.7–50)  |                   |                   |
| Body image        |                  |                   |                   |                  |                   |                   |                  |                   |                   |
| Early             | 88.9 (66.7–100)  | 0 (–11.1, 0)      | 0.715             | 88.9 (77.8–100)  | 0 (0, 11.1)       | 0.364             | 94.4 (77.8–100) | 100 (88.9–100)   | 0.502             |
| Late              | 77.8 (66.7–100)  |                   |                   | 88.9 (66.7–100)  |                   |                   | 100 (88.9–100)  |                   |                   |

*Two-sample Hodges–Lehmann (H–L) estimator with 95 per cent asymptotic confidence limits in parentheses. EORTC, European Organisation for Research and Treatment of Cancer. †Wilcoxon rank sum test for difference between early and late closure.

than the reference group, with physical functioning scoring the highest among the dimensions.

EORTC QLQ-C30 and QLQ-CR29 scores were comparable between intervention and control groups. Emotional functioning was lower in the early closure group at 3 and 6 months, but similar to the late closure group at 12 months (Table 3). No statistically significant differences were seen in the dimensions of the QLQ-CR29 questionnaire (Table 4).

Discussion

In this RCT no significant differences were observed in HRQOL within 12 months after rectal resection for cancer when early and late closure of temporary ileostomy were compared. Global QOL generally improved later in the follow-up period (6–12 months), and at 12 months the results were comparable, not only between the two groups but also with respect to both age-matched reference populations and previous findings. Although there was a tendency for improvement over time in global QOL and role functioning, no clinically significant changes were seen in QLQ-C30 scores. The definition of a clinically significant change over time was based on the suggestion that a difference of 5–10 points be considered a ‘little change’ and a difference of 10–20 points a ‘moderate change’. When comparing the SF-36® scores with Swedish reference data, a general improvement was seen during the follow-up interval.
No baseline data for preoperative assessment were available, owing to the fact that the patients were enrolled and randomized after the rectal resection. This is considered a weakness in the evaluation of HRQOL. Even though reference data were available, there was no opportunity to investigate the development and changes in HRQOL from preoperative to postoperative values. In addition, considering the length of time needed for recovery after rectal cancer surgery, follow-up at 18 and 24 months might have been of value to observe any further development and potential improvement in HRQOL.

The lack of difference between the two groups differs somewhat from the findings of previous prospective studies, which have reported that patients with a temporary stoma may suffer from impaired HRQOL in comparison with patients who had undergone a similar operation but without a covering stoma, such as a high anterior resection. However, the results of previous studies are contradictory. A Danish study suggested that a temporary stoma left patients with feelings of uncertainty, that closure of the stoma was seen as a crucial event, and that knowing the date for closure was important. A prospective study found improved global QOL following stoma reversal after low anterior resection for rectal cancer, and physical function, as measured by both the QLQ-C30 and SF-36® questionnaires, was also significantly improved. However, a prospective interview study reported no change in QOL following closure of a temporary stoma after rectal cancer surgery, and the patient’s personality rather than clinical variables has a strong and lasting influence on QOL. As suggested in a review article from 2011, closure of the stoma and prompt redirection of intestinal contents to the rectum 3–6 months after rectal resection might be considered to be a cause of negative impact on patients’ physical, social and psychological health for several months. Gastrointestinal symptoms, such as increased stool frequency, urgency, diarrhoea and persistent problems including low anterior resection syndrome, do not occur in the presence of a temporary stoma. Consequently, stoma reversal might result in the appearance of these symptoms. Although this was not observed in the present study, this could be because of the small size of the cohort. In the COLOR II trial, patients with rectal cancer appeared to need a longer time to recover compared with those with colonic cancer. This could perhaps explain the lack of difference between the groups in the present study, as both involved extensive surgery for rectal cancer, where timing of the stoma closure is not reflected in the HRQOL follow-up.

The EASY trial found that it was safe and advantageous to close the loop ileostomy early in patients with no clinical or radiological signs of anastomotic leakage. However, the present study did not find a link between this clinical advantage and patients’ HRQOL.

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