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## Systematic Screening for Late Sequelae after Colorectal Cancer - a Feasibility Study

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## Systematic Screening for Late Sequelae after Colorectal Cancer - a Feasibility Study

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## **Abstract**

**Aim:** The aim of this study was to test the feasibility of a new method for systematic screening for late sequelae following colorectal cancer treatment.

**Method:** Patients with colorectal cancer from five Danish hospitals were invited to complete a survey about late sequelae at 3, 12, 24 and 36 months after surgery as part of their follow-up. The survey consisted primarily of validated tools, supplemented by a few *ad hoc* items, measuring bowel, urinary and sexual dysfunction, pain and quality of life and an additional question regarding request for contact. Patients completed surveys electronically or on paper.

**Results:** Of the 1,721 invited patients, 1,386 (80.5%) were included (1,085 with colon cancer and 301 with rectal cancer) of whom 72.5% responded electronically. Patients responding electronically were 7.6 years younger than those responding on paper ( $p < 0.001$ ). Since some patients answered more than once, the dataset consisted of 2,361 surveys. Patients with colon cancer requested phone contact in 19.0% of the surveys, and 8.4% were referred to treatment for late sequelae, primarily bowel dysfunction. Among patients with rectal cancer, 30.8% requested phone contact, and 16.2% were referred for treatment of late sequelae, mainly due to bowel and sexual dysfunction.

**Conclusion:** This is the first paper investigating a new method of systematic screening for late sequelae following colorectal cancer using electronic patient-reported outcome measures. The study shows that in the Danish population, a high response rate can be obtained with this method, and that close to 3/4 of patients respond electronically. Patients with rectal cancer had a higher need for phone contact and treatment of late sequelae than patients with colon cancer.

**“What does this paper add to the literature?”**

Late sequelae are highly prevalent and have a great impact on colorectal cancer patients’ quality of life. Still, these problems attract only very limited attention in current follow up programs. In this paper a new model for systematic detection and management of late sequelae is presented, and its feasibility is tested.

## Introduction

Colorectal cancer (CRC) is the third most common cancer worldwide, with an estimated incidence of more than 1.8 million cases in 2018(1). In Denmark, the mean yearly incidence of CRC is about 5,000, and the 5-year relative survival rate is 64% for males and 67% for females (2). Today, more than 36,000 living Danes have survived CRC (2). Due to the increasing incidence of CRC and continuous improvements in survival rates, the number of CRC survivors is expected to rise in the future. This calls for heightened attention to survivorship care.

During the past decade, a growing body of literature has clearly documented that late sequelae (LS) after CRC are highly prevalent. Studies have shown a high prevalence of bowel, urinary and sexual dysfunction, as well as chronic pain (3-10) and chemotherapy-induced neuropathy (11). Such LS have a significant negative impact on patients' quality of life (QoL)(12-15).

Nevertheless, follow-up after CRC continues to focus mainly on detection of local and distant recurrence. This was well documented in a recent review of current European guidelines for post-CRC follow-up. The review showed significant variation in terms of follow-up intervals and methods of follow-up, and that identification and treatment of LS received only very limited attention (Fig 1)[Fig 1 near here]. The authors found that management of LS was mentioned in only 12 of the 21 guidelines and was recommended explicitly in only four (16). Moreover, the consensus was that structured follow-up should be offered *only* to patients who could/would receive further treatment if recurrence was detected. This implies a risk that patients unfit for treatment of a recurrence are excluded from early identification and management of LS. Another recent review investigated the extent to which practice guidelines for CRC and anal cancer include recommendations for managing LS (17). Recommendations were found in only 13 out of 51 guidelines, which underlines the need for a stronger focus on management of LS following CRC.

Despite growing recognition of the high prevalence of LS and its severe QoL impact, LS are still poorly managed by the healthcare system(18, 19). For example, in 2015 the Danish Health and Medicine Authority published new guidelines for follow-up after CRC that explicitly include management of LS (20). However, no standardized methods for identifying and treating LS have yet been implemented in Denmark. Consequently, management of LS following CRC remains

random and often completely lacking, leaving CRC survivors with a variety of undetected and untreated symptoms(21). Since some LS can be treated by relatively simple means, a large group of patients could potentially benefit substantially from incorporating systematic screening for LS in the follow-up program after CRC.

Therefore, the aim of this study was to develop a new modality for systematic screening for LS after CRC via electronic patient-reported outcome measures (ePROMs) and investigate its feasibility. With this new method, colorectal cancer patients complete online surveys regarding late sequelae at 3, 12, 24, and 36 months after surgery. The patients indicate whether or not they want to be contacted by phone to receive information regarding treatment options, and they are referred to relevant standard treatments if requested.

We hypothesized that a) a response rate of > 75% could be obtained, b) two thirds of the participants would be able to respond electronically and c) patients with rectal cancer (RC) would have a higher need for contact and treatment of LS than patients with colon cancer (CC).

## **Methods**

### ***Participants***

Patients older than 18 years, with CRC treated at the surgical departments in Aalborg, Hjoerring, Randers, Viborg and Aarhus, Denmark were eligible for inclusion if treated for CRC with resectional surgery with or without chemo-/radiotherapy. Exclusion criteria were living in another region of Denmark and difficulties either understanding participant information or completing surveys due to linguistic barriers or cognitive impairment. Furthermore, patients undergoing local excision were excluded since they were not expected to suffer from any significant LS. Also excluded were patients with advanced tumours, defined as tumour growth beyond the mesorectal/mesocolic fascia, histopathological pT4 tumour with invasion of adjacent structures or peritoneal carcinomatosis.

All patients included in the study gave informed consent and the study was registered in the Central Denmark Region's register of research projects (no. 1-16-02-972-17).

### ***Recruitment and Timing of Surveys***

The study design is illustrated in Fig 2 [Fig 2 near here]. The first CC patient was invited on 16 April 2018. A cohort of patients with CC having undergone surgery within the past three years

before the study started were identified via local registries and invited to participate when reaching one of the chosen time points (3, 12, 24 or 36 months after surgery). Patients with CC treated after study start were prospectively invited 3 months after surgery.

Inclusion of patients with RC started on 1 November 2018. Patients with RC were included only prospectively at 3 months after surgery to avoid interfering with an ongoing randomized clinical trial (RCT) involving patients with RC treated prior to 1 August 2018(22). Thus, patients with CC entered the study at different time points (3, 12, 24 and 36 months after surgery), while all patients with RC entered 3 months after surgery.

Once included, patients were requested to complete the survey at all future time points at 3, 12, 24 and 36 months after surgery. Patients who had a temporary diverting stoma also completed the survey 3 months after the stoma was reversed. The last patient included in the analyses of this paper was invited on 7 September 2020.

REDCap (Research Electronic Data Capture), a secure web application, was used for collecting and managing patient reported outcome measures (PROMs)(23).

An invitation with a link to an online survey was sent to a secure digital mailbox (“eBoks”) linked to Danish citizens’ civil registration number and used for communication between citizens and authorities, including the healthcare system(24). Non-users of the internet received a paper version of the questionnaire, along with a prepaid return envelope, by ordinary mail.

In case of no response to the invitation, two reminders were sent 2 weeks apart. Included patients having completed at least one survey but not responding to the subsequent survey also received two reminders 2 weeks apart. If no response was obtained, data were registered as missing. Still, the patient was invited to complete the survey again at the next time point unless withdrawal from the study was explicitly stated.

### ***Patient-Reported Outcome Measures (PROMs)***

The PROMs included in the surveys are shown in Table 1 [Table 1 near here]. Short but adequate screening tools were preferred for collection of PROMs to minimize any inconvenience for patients. The survey covered only the most prevalent LS following CRC for which the participating centres offered treatment options. Questions about rare sequelae and sequelae for which no available treatment options were available were excluded.

Since patients with CC primarily report bowel dysfunction, the survey for this group included PROMs covering a variety of symptoms related to bowel function (10, 25). Patients with RC, on the other hand, undergo surgery in the deep pelvis and some also receive neoadjuvant chemo-/radiotherapy. Therefore, these patients suffer from a wider range of LS including urinary, bowel and sexual dysfunction as well as chronic pain (7, 26-29). All these domains were covered by the selection of PROMs for patients with RC.

LARS, Wexner and St Mark's scores (8, 30, 31) have several overlapping items with minor differences in response category wordings. To avoid repetition of items, the response categories were adapted to facilitate calculation of score values for each of the three scores without repeating any items. For both groups of patients, we added a few *ad hoc* items and also a QoL score (EQ5D-5L)(32) to facilitate analysis of correlations between LS and QoL in future studies (Table 1).

### ***Identifying Patients with LS and a Need for Treatment***

Although score values were calculated for all tools included in the survey, the values did not determine whether a patient was contacted or not. Patients were contacted exclusively on the basis of their answer to the final survey question: *“Do you wish to be contacted to discuss treatment options for any late sequelae?”* This option was offered to all patients at 12, 24 and 36 months after surgery. Additionally, patients with RC were offered to be contacted as soon as 3 months after surgery/stoma reversal, since previous studies have shown that bowel dysfunction at 3 months predicts bowel dysfunction at 12 months in these patients. Hence, in a large proportion of patients with RC, bowel dysfunction will not resolve spontaneously within the first year (13) wherefore it seems reasonable to offer treatment at this early stage.

Referral to treatment for LS was based on patients' subjective needs and available treatment options - independently of the PROM score values.

To obtain information regarding any missing domains considered significant by the patients, they were also asked *“Do you suffer from any late sequelae NOT covered by this questionnaire?”* with a free text response option.

### ***Evaluation of Surveys and Referral to Treatment***

In collaboration with the “Clinic for Treatment of Late Sequelae after Pelvic Organ Cancer” at Aarhus and Aalborg University Hospitals, the study group developed a well-defined referral and

treatment strategy for LS. The treatments offered are non-experimental standard treatments, some of which are described in detail elsewhere (33, 34)

All completed surveys were evaluated by a health care professional, i.e. a specialized nurse or a doctor. If a patient wished to be contacted, the health care professional called the patient within 2 weeks to obtain more detailed information about the symptoms and then presented available treatment options. Patients interested in the proposed treatment were referred to relevant specialists (Fig 2). Patients continued to receive surveys as planned regardless of any treatment offered during the follow-up period.

## Results

### *Invited Patients*

A total of 1,721 patients (1349 CC, 372 RC) fulfilled the inclusion criteria and received an invitation to participate in the study. The proportion of males was 54.4%.

### *Included vs. not-included patients*

Of the 1,721 invited patients, 1,386 were included (1,085 CC, 301 RC), resulting in an overall inclusion rate of 80.5%. Figure 3 shows at what time point after surgery patients were invited and the corresponding inclusion rates. Out of the 335 (19.5%) not-included patients, 140 (41.8%) explicitly declined to participate, while the remaining 195 (58.2 %) did not respond at all.

Inclusion rates and number of reminders per age group are shown in Table 2 [Table 2 near here].

Among the 1,386 included patients 1,018 (73.5%) accepted participation after having received the initial invitation to the study, while 220 (15.9%) were included after one reminder and 148 (10.7%) after two reminders.

Not-included patients were significantly older than included patients (73.0 years vs. 69.9 years,  $p < 0.001$ ). The inclusion rate was slightly higher for males (82.0%) than for females (78.8%), but this difference was not statistically significant ( $p = 0.11$ ). The inclusion rate was independent of cancer type ( $p = 0.88$ ), centre ( $p = 0.96$ ) and of time between surgery and inclusion in the study ( $p=0.20$ ).

### ***Mode of Administration***

Mode of administration per age group is presented in Table 2.

Most patients responded electronically (72.5%). The mean (sd) age of patients responding electronically was 67.9 (10.34) years, while patients responding on paper were 75.5 (9.72) years old, i.e., a difference of 7.6 years ( $p < 0.001$ ). The proportion of patients responding electronically was negatively correlated with age; however, even among patients  $>75$  years, 53.6% completed the survey electronically.

### ***Number of Completed Surveys***

Of the 1,386 included patients, 21 have not yet completed the first survey. Among the remaining patients, 551 have completed the survey once, 637 twice, 172 thrice and five patients have completed the survey four times, resulting in a total of 2,361 completed surveys (1,855 CC, 506 RC).

### ***Actions Taken***

Table 3 shows the number of completed surveys, phone contacts and referrals at each time point for patients with CC and patients with RC [Table 3 near here]. Note that although 654 patients with CC completed the survey 3 months after surgery and seven patients with CC completed the survey 3 months after stoma reversal, they were not contacted at this time point; hence, these surveys are not included in Table 3. Therefore, Table 3 includes the results of 1,194 surveys completed by patients with CC and 506 surveys completed by patients with RC.

In the 1,194 CC surveys, contact was requested by 227 (19.0%), and a total of 100 (8.4%) surveys led to referral for treatment of LS, primarily bowel dysfunction. In the 506 RC surveys, contact was requested by 156 (30.8%) and a total of 82 (16.2%) surveys led to referral for treatment of LS, mainly bowel and sexual dysfunction. The types of sequelae leading to referral are shown in Table 3.

The proportion of patients contacted and referred to treatment for LS was significantly higher for patients with RC than for patients with CC ( $p < 0.001$ ) (Fig 4) [Fig 4 near here]

### ***Exhaustiveness of the Survey***

Out of the 1,365 CRC patients who completed at least one survey, 375 (27.5%) ticked “Yes” at the question “Do you suffer from any late sequelae NOT covered by this questionnaire?” at one or

more occasions. For patients with CC this proportion was 26.4%; for patients with RC, it was 31.5%. Since some patients chose this option at several surveys, a total of 503 free-text fields were available for analysis. A qualitative analysis of the responses revealed that the patients suffered from a wide variety of LS not covered sufficiently or not at all in the survey. However, each type of LS was mentioned only by a limited number of patients (Table 4). Please note that since some patients described more than one type of LS, the total number of LS exceeds the total number of patients who ticked “Yes” to the question. If a patient described the same type of LS at several surveys, this was counted only once.

LS reported by at least 12 patients are presented separately, while LS mentioned by fewer patients were pooled into a common category of “Other sequelae” (for example respiratory, oedema, dizziness, haemorrhoids, scar/intra-abdominal adhesions).

Although bowel dysfunction was actually covered in the survey for both patients with CC and RC, this category was still mentioned by 6.7% of the patients with CC and by 4.4% of the patients with RC. Thus, these patients apparently felt that their bowel function was not covered sufficiently. Chemotherapy-induced neuropathy was the second most frequently reported late sequela not covered in the questionnaire, followed by pain, fatigue/sleep disturbances and hernias.

## **Discussion**

This is the first study showing that systematic screening for LS after CRC via electronic PROMs is feasible. With this method, we obtained a very high response rate (80.5%), and 72.5% of the surveys were completed electronically.

A statistically significantly higher proportion of patients with RC than those with CC requested contact and were referred to treatment for LS ( $p < 0.001$ ). Among patients with CC, 19.0% requested phone contact and 8.4% were referred for treatment of LS; among patients with RC, 30.8% requested phone contact and 16.2% were referred for treatment of LS.

Patients included in this study were simultaneously enrolled in a standard follow-up program which theoretically should not only detect recurrence but also include management of LS (20). However, the results of the present study show that the current standard follow-up is not efficient but leaves a proportion of patients with undetected and untreated LS. This underlines the urgent need for a more systematic approach, ensuring that LS are detected and managed sufficiently.

Our previous attempts to implement screening for LS at follow-up visits in the outpatient clinic were challenged by the lack of time in daily clinical practice and a high number of surgeons and nurses involved, which led to a relatively low inclusion rate. Therefore, we developed the method presented in this paper. Major advantages of this new approach were, firstly, that it was managed by only one or two people at each centre; secondly, 72.5% of the responses were entered electronically by the patients; and, finally, we *a priori* developed clear referral strategies and well-defined treatment algorithms for LS.

As expected, a larger proportion of patients with RC than those with CC was referred to treatment of LS. However, a minor part of this difference could be explained by the fact that patients with CC were not offered contact at 3 months after surgery. We chose this strategy because we were interested in investigating spontaneous improvement in bowel symptoms within the first year after CC surgery. Future analyses of our data will explore this further, and the results will be presented in a separate paper.

While close to three out of four patients completed the survey online, the remaining patients preferred a paper version of the questionnaire, mainly because they were not internet users. More time was spent on handling questionnaires and managing the survey distribution for paper-based questionnaires than for electronically distributed questionnaires. However, the group of non-internet users is expected to decrease significantly within the next few years. In the autumn of 2020, 88.5% of Danish citizens aged 65-74 years received digital mail from public authorities (e-Boks); the corresponding percentage for citizens aged 75-84 years was 69.1% (35). Thus, the proportion of non-internet users is likely to decrease spontaneously.

A limitation of the new method presented in this paper is that one out of five invited patients did not wish to participate in the study. Their reason for non-participation is unclear; however, it is important to acknowledge that the new method is not suitable for all CRC patients. We expect that a small subgroup of Danish patients will still need a tailored follow-up program with pre-scheduled phone calls and/or visits in the outpatient clinic to ensure that late sequelae are effectively detected and managed in all patients regardless of age, cognitive function, and level of health literacy. Furthermore, the generalisability of our results is limited to cultures with similar levels of educational attainment and health literacy, availability of internet access and a similar proportion of patients owning a computer, a smartphone or another mobile device. However, since the proportion of patients with internet access and owning smartphone is rapidly increasing worldwide, CRC patients in low-income countries can potentially benefit from an adapted version

of the method proposed in this paper. By identifying LS electronically, time and money spent on travelling to the hospital/clinic can be spared. Clearly, treatment options for LS must be available, if the aim is not merely to collect data for research purposes, but also to improve the individual patient's QoL.

Another limitation of the proposed method is that it was developed for non-advanced CRC patients only. The concept is likely to be advantageous in the follow-up of CRC patients with advanced disease, but this requires different survey contents and timing. Therefore, we are currently developing and testing a similar method for systematic screening for LS after advanced CRC, and will start recruitment in the spring of 2021.

More than one fourth of the patients used the free-text field regarding LS *not* covered by the survey. Their responses indicated that it might be relevant to add questionnaires regarding pain for patients with CC, and herniation for both patients with CC and patients with RC, since treatment options are available for these types of LS. Herniation should be evaluated by the colorectal surgeon, and the treatment options should be discussed with the patient. In most cases, conservative treatment will be the best solution, and surgery will be relevant only in a few cases; however, a clarification of which treatment options exist, and what its related risks are is likely to improve patients' QoL.

Medical treatment of pain can be managed by the colorectal surgeon in some cases. If not, referral to a pain clinic offering specialised management is required.

Neuropathies, fatigue and mental/cognitive issues were also reported, and these domains should be included as soon as effective treatment options become available.

In this study, patients who were identified with LS and requested treatment were offered treatment by various specialists depending on the type of LS. Previous studies have indicated that transanal irrigation and sacral nerve stimulation may improve bowel function after rectal cancer (36, 37), and treatment of bile acid malabsorption and small intestinal bacterial overgrowth can improve bowel dysfunction after colonic cancer (33). However, it should be noted that the vast majority of treatments for LS following CRC lack hard evidence (37, 38). Therefore, we are currently systematically measuring the effect of all treatments offered to our LS patients. All patients with CRC undergoing treatment of bowel, urinary and sexual dysfunction complete electronic PROMs at baseline and up to 3 years after end of treatment, and the analyses of these comprehensive datasets will be published in later papers.

The method used for systematic screening for LS after CRC presented in this paper is currently used in a prospective, multicentre study investigating the prevalence of LS after CRC and the patients' subjective need for treatment. Recruitment of patients is ongoing, and more Danish centres will be enrolled during 2020. The high number of collected data, covering a wide variety of late sequelae, will be analysed with relevant clinical variables from the Danish registries, and the results of these comprehensive analyses will be presented for colon- and rectal cancer patients in separate papers.

Our current standard follow-up program for patients with RC includes at least 5-6 scheduled clinical visits. However, evidence of the effect of frequent clinical visits on the oncological outcome/mortality is scarce(16). The new method presented in this paper can potentially substitute current standard follow-up schemes if items on signs of recurrence are added. Implementing the new method in clinical practice will not only spare patients unnecessary, inefficient and time-consuming clinical visits and thereby lower healthcare costs but will also ensure that LS are detected not at random, but systematically in all CRC patients.

In conclusion, the proposed method for systematic screening of patients with CRC for LS with electronic PROMs is feasible. By systematically identifying and treating LS following CRC, it is expected that functional outcomes and QoL can be improved significantly in this group of patients. This hypothesis is being investigated in ongoing studies.

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|  | Questionnaire (reference) / “ <i>ad hoc</i> ” single items   | Items | Colon | Rectum |      |
|--|--|-------|-------|--------|------|
|  |  |       |       | Female | Male |
| Bowel function, no stoma   | Low Anterior Resection Syndrome Score (8)  | 10    | ✓     | ✓      | ✓    |
|  | Wexner Incontinence Score (30)   |       | ✓     | ✓      | ✓    |
|  | St Mark’s Incontinence Score (31)  |       | ✓     | ✓      | ✓    |
|  | Bristol Stool Chart (39)   | 1     | ✓     | ✓      | ✓    |
|  | Patient Assessment of Constipation Symptoms (40)   | 12    | ✓     |        |      |
|  | <i>“Do you take any medicine for constipation?”</i>  | 1     | ✓     | ✓      | ✓    |
|  | <i>“Do you take any fiber supplement?”</i>   | 1     | ✓     | ✓      | ✓    |
|  | <i>“Do you have bowel movements during the night?”</i>   | 1     | ✓     |        |      |
|  | <i>“How would you evaluate your bowel function over the past 4 weeks?”</i>   | 1     | ✓     | ✓      | ✓    |
| <i>“Overall, how much does your bowel function affect your quality of life?”</i> | 1  | ✓     | ✓     | ✓      |      |
| Bowel function, with stoma   | Colostomy impact score (41)  | 7     | ✓     | ✓      | ✓    |
|  | <i>“How would you evaluate your bowel function over the past 4 weeks?”</i>   | 1     | ✓     | ✓      | ✓    |
|  | <i>“Overall, how much does your bowel function affect your quality of life?”</i>                                     | 1     | ✓     | ✓      | ✓    |
| Diet   | <i>6 ad hoc questions regarding diet</i>   | 6     | ✓     |        |      |
|  | Memorial Sloan Kettering Cancer Center Bowel Function Index (dietary scale) (42)                                     | 4     |       | ✓      | ✓    |
| Urological function  | ICIQ Female Lower Urinary Tract Symptoms (43)  | 12    |       | ✓      |      |
|  | ICIQ Male Lower Urinary Tract Symptoms (44)  | 13    |       |        | ✓    |
|  | <i>“Do you experience pain or a burning sensation when urinating?”</i>   | 1     |       | ✓      | ✓    |
|  | <i>How would you evaluate your urinary function over the past four weeks?</i>  | 1     |       | ✓      | ✓    |
| Pain   | Rectal Cancer Pain Score (28)  | 6     |       | ✓      | ✓    |
|  | <i>“Overall, how much have you been affected by pain over the past four weeks?”</i>                                  | 1     |       | ✓      | ✓    |
| Sexual function  | International Index for Erectile Function (45)   | 5     |       |        | ✓    |
|  | Rectal Cancer Female Sexuality Score (Sexually active only)(15)  | 7     |       | ✓      |      |
|  | <i>“Why did you interrupt your sexual life after the diagnosis?”</i><br>(If interrupted sexual life after diagnosis) | 1     |       | ✓      |      |
|  | <i>“How would you evaluate your sexual function over the past four weeks?”</i>                                       | 1     |       | ✓      | ✓    |
| Quality of life  | European Quality of Life – 5 Dimensions (EQ5D)(32)   | 5     | ✓     | ✓      | ✓    |
|  | <i>“Overall how would you evaluate your quality of life over the past 4 weeks?”</i>                                  | 1     | ✓     | ✓      | ✓    |
| Missing items  | <i>“Do you have any late sequelae from your bowel cancer treatment that are NOT covered in this questionnaire?”</i>  | 1     | ✓     | ✓      | ✓    |
| Need for treatment   | <i>“Do you wish to be contacted to discuss possibilities for treatment of any late sequelae?”</i>                    | 1     | ✓     | ✓      | ✓    |

Table 1. Tools used in the survey. Tools with a reference are published scores, while the items in “italics” are *ad hoc* items.

Table 2 Inclusion rates, number of reminders and mode of administration per age group.

| Invited patients (n=1721) |              |              | Included patients            |                    |              |                                  |             |             |
|---------------------------|--------------|--------------|------------------------------|--------------------|--------------|----------------------------------|-------------|-------------|
|                           |              |              | Number of reminders (n=1386) |                    |              | Mode of administration (n=1365)* |             |             |
| Age group                 | Included     | Not included | Age group                    | Initial invitation | One reminder | Two reminders                    | Electronic  | Paper       |
| <65, n(%)                 | 400 (85.1%)  | 70 (14.9%)   | <65, n(%)                    | 284 (71.0%)        | 67 (16.8%)   | 49 (12.3%)                       | 336 (85.3%) | 58 (14.7%)  |
| 65-75, n(%)               | 520 (83.2%)  | 105 (16.8%)  | 65-75, n(%)                  | 380 (73.1%)        | 73 (14.0%)   | 67 (12.9%)                       | 407 (79.5%) | 105 (20.5%) |
| >75, n(%)                 | 466 (74.4%)  | 160 (25.6%)  | >75, n(%)                    | 354 (76.0%)        | 80 (17.2%)   | 32 (6.9%)                        | 246 (53.6%) | 213 (46.4%) |
| Total, n(%)               | 1386 (80.5%) | 335 (19.5%)  | Total, n(%)                  | 1018 (73.4%)       | 220 (15.9%)  | 148 (10.7%)                      | 989 (72.5%) | 376 (27.6%) |

\* 21 patients have not yet responded to the survey

Table 3 Actions taken and type of sequelae registered, based on 1,700 completed surveys.

|   | Colon cancer patients                      |  |                       |   | Rectal cancer patients |             |                    |            |                                 |
|---|--|--|-----------------------|---|------------------------|-------------|--------------------|------------|---------------------------------|
|   | 12 mo                                      | 24 mo                                    | 36 mo                 | Total   | 3mo                    | 3 mo ASR*   | 12 mo              | 24 mo      | Total                           |
| <b>Surveys (n)</b>                        | 527  | 377                                      | 290                   | 1,194   | 295                    | 36          | 161                | 14         | 506                             |
| <b>Patients contacted by phone (n, %)</b> | 100 (19.0%)                                | 81 (21.5%)                               | 46 (15.9%)            | 227 (19.0 %)  | 88 (29.8 %)            | 18 (50.0 %) | 47 (29.2 %)        | 3 (21.4 %) | 156 (30.8 %)                    |
| <b>Patients referred (n, %)</b>           | 40 (7.6 %)                                 | 39 (10.3 %)                              | 21 (7.2 %)            | 100 (8.4 %)   | 51 (17.3 %)            | 13 (36.1%)  | 17(10.6 %)         | 1 (7.1 %)  | 82 (16.2 %)                     |
| <b>Referrals** due to:</b>                |  |  |                       |   |                        |             |                    |            |                                 |
| <b>Bowel dysfunction (n)</b>              | 34   | 33                                       | 17                    | 84  | 17                     | 11          | 8                  | -          | 36                              |
| <b>Sexual dysfunction (n)</b>             | -  | -  | -                     | -   | 27                     | 2           | 4                  | -          | 33                              |
| <b>Urological dysfunction (n)</b>         | -  | 1  | -                     | 1   | 12                     | 2           | 3                  | -          | 17                              |
| <b>Pain (n)</b>                           | 5  | 5  | 1                     | 11  | 3                      | -           | -                  | 1          | 4                               |
| <b>Other (n)</b>                          | 4  | 4  | 3                     | 11  | 4                      | -           | 2                  |            | 6                               |
| <b>Other, type (n)</b>                    | Fatigue:1<br>Stoma:1<br>Skin:1<br>Mental:1 | Fatigue:2<br>Bleeding:1<br>Hemorrhoids:1 | Fatigue:1<br>Hernia:2 | Fatigue: 4<br>Hernia:2<br>Stoma:1<br>Skin:1<br>Mental:1<br>Bleeding: 1<br>Hemorrhoids:1 | Stoma: 3<br>Hernia:1   |             | Stoma:1<br>Gynae:1 |            | Stoma: 4<br>Hernia:1<br>Gynae:1 |

\*ASR: After Stoma Reversal, \*\*Some patients were referred for more than one type of sequelae

Table 4 Late sequelae not covered sufficiently or not at all in the survey, according to the patients

|  | CC patients<br>(n=1070) | RC patients<br>(n=295) |
|--|-------------------------|------------------------|
| “Do you suffer from any late sequelae NOT covered by this questionnaire” Yes, n (%)* | 282 (26.4 %)            | 93 (31.5 %)            |
| Bowel dysfunction, n   | 72 (6.7%)               | 13 (4.4%)              |
| Chemotherapy induced neuropathy, n   | 64 (6.0%)               | 14 (4.7%)              |
| Pain, n  | 47 (4.4%)               | 19 (6.4%)              |
| Fatigue/sleep disturbance, n   | 43 (4.0%)               | 13 (4.4%)              |
| Hernia, n  | 26 (2.4%)               | 12 (4.1%)              |
| Skin/mucosa/teeth, n   | 24 (2.2%)               | 8 (2.7%)               |
| Mental/cognitive problems, n   | 19 (1.8%)               | 10 (3.4%)              |
| Loss of appetite/nausea/weight loss, n   | 10 (0.9%)               | 0 (0%)                 |
| Body image, n  | 10 (0.9%)               | 3 (1.0%)               |
| Urinary dysfunction, n   | 9 (0.8%)                | 3 (1.0%)               |
| Sexual dysfunction/worries, n  | 5 (0.5%)                | 7 (2.4%)               |
| Other sequelae, n  | 50 (4.7%)               | 25 (8.5%)              |

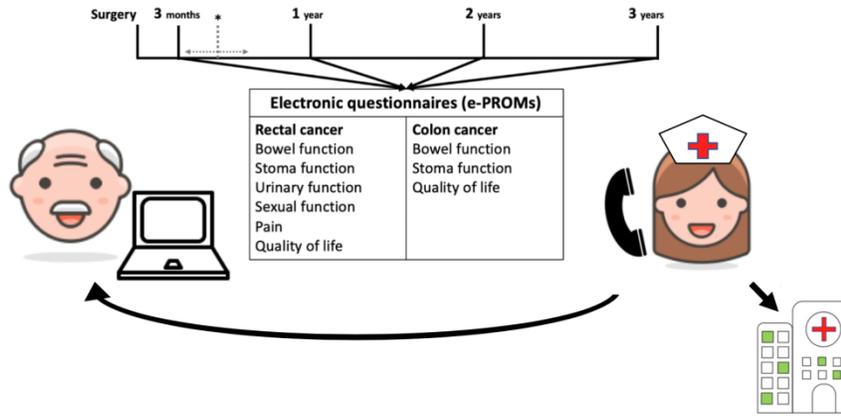
\*Number of patients who ticked “Yes” at one or more surveys.

*Late sequelae after cancer treatment are health issues that occur during primary treatment and persist to become chronic, or that occur and manifest months to years after treatment is completed. The sequelae can include both new primary cancers and physical, psychological or social changes resulting from the cancer disease and/or from the treatment*

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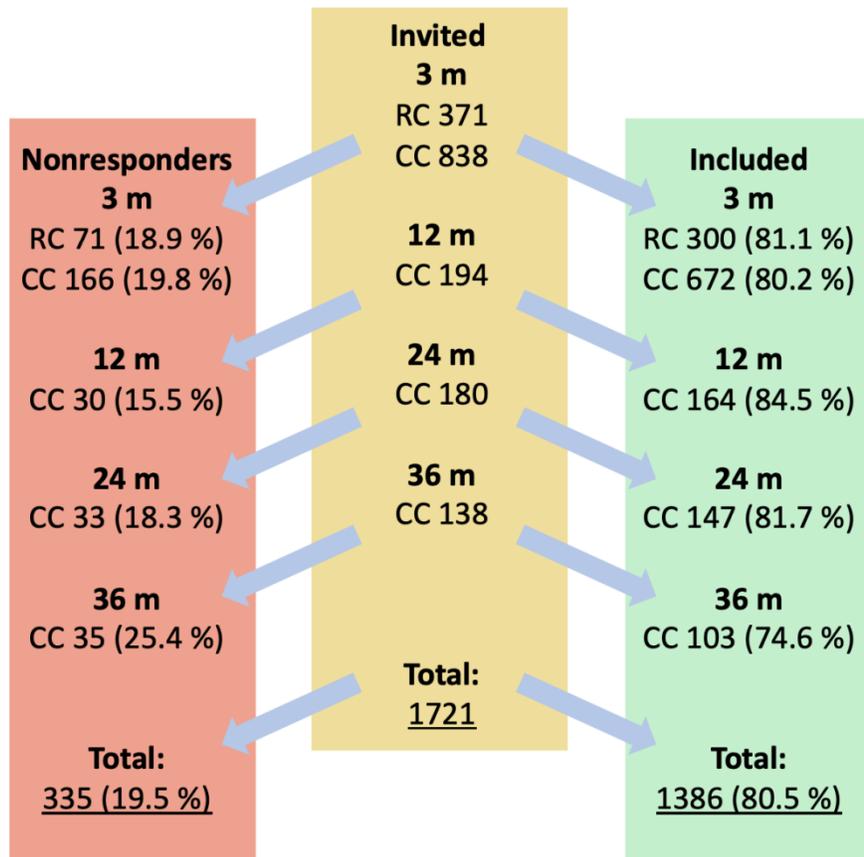
### Systematic screening for late sequelae after CRC

The patient completes survey → The nurse evaluates the response → The nurse calls the patient if he/she requests contact →  
 The nurse and the patient discuss treatment options → The nurse refers the patient to the relevant department if he/she wants treatment



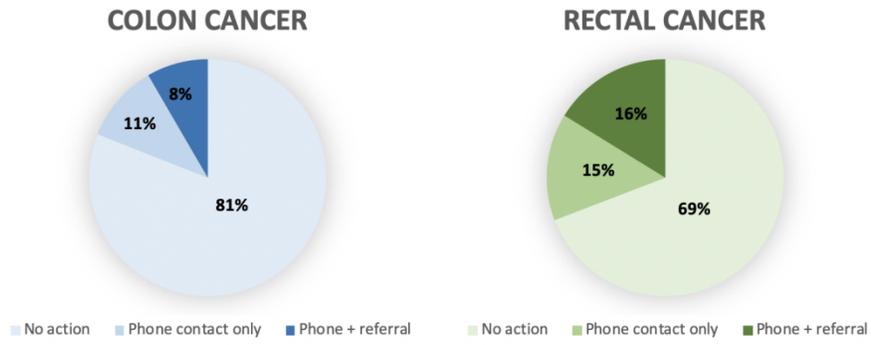
\*Patients with a temporary diverting stoma complete the survey 3 months after the stoma reversal

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All patients with rectal cancer (RC) were invited 3 months after surgery while patients with colon cancer (CC) were invited 3, 12, 24, or 36 months after surgery.

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