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### Changes in health-related outcomes among colorectal cancer patients undergoing inpatient rehabilitation therapy

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1 **Changes in health-related outcomes among colorectal cancer patients**  
2 **undergoing inpatient rehabilitation therapy: A systematic review of**  
3 **observational and interventional studies**

4  
5 **Running title:** Inpatient rehabilitation therapy in colorectal cancer patients  
6

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1 **Changes in health-related outcomes among colorectal cancer patients**  
2 **undergoing inpatient rehabilitation therapy: A systematic review of**  
3 **observational and interventional studies**

4  
5 BACKGROUND: Colorectal cancer (CRC) and its treatment can lead to several  
6 physical and psychosocial impairments. Cancer rehabilitation aims to reduce  
7 morbidity and improve quality of life. The objective of this review was to  
8 summarize and evaluate evidence on changes in health-related outcomes among  
9 CRC patients undergoing inpatient rehabilitation therapy and on effectiveness of  
10 such treatment.

11 MATERIAL AND METHODS: We conducted a systematic literature search  
12 including the electronic databases Pubmed and Web of Science to find  
13 observational and interventional studies, which investigated changes in health-  
14 related outcomes among CRC patients undergoing multidisciplinary inpatient  
15 rehabilitation programs or treatment effects. Study findings were synthesized  
16 narratively.

17 RESULTS: Eleven studies were eligible and included in this review. Eight  
18 patient cohort studies addressed outcomes such as physical and functional status,  
19 fecal incontinence, anxiety and depression and quality of life. Positive changes  
20 during rehabilitation therapy were observed for physical health (functional and  
21 physical status, fecal incontinence) and several dimensions of quality of life.  
22 Study findings concerning anxiety and depression were not conclusive. Studies  
23 that additionally conducted long-term follow-ups indicated that the improved  
24 health status after rehabilitative treatment waned over time. One RCT reported no  
25 effect of inpatient rehabilitation on distress and two randomized trials reported  
26 effects of exercise intensity on oxidative stress and immune response. Sample  
27 sizes were low (<100 included CRC patients) in eight studies and only the RCT  
28 included a comparison group (non-rehabilitants).

29 CONCLUSION: The scientific evidence level was very limited. Due to the lack  
30 of comparison group in most studies, we were only able to evaluate changes  
31 during / after inpatient rehabilitation therapy but not effectiveness of treatment.

1           However, study findings suggest that physical health and functional  
2           independence improve during inpatient rehabilitation, but improvements wane  
3           over time. Further large representative studies, in particular RCTs with long-term  
4           follow-up, are essential to evaluate the effectiveness of inpatient rehabilitation  
5           and identify determinants of treatment success.

6           **Keywords:** inpatient rehabilitation; colorectal cancer; functional status; fecal  
7           incontinence; quality of life

8

## 1 **Introduction**

2 Colorectal cancer (CRC) is the third most frequent cancer worldwide with estimated 1.8  
3 million new cases in 2018 [1]. The current 5-year relative survival is about 63 % in  
4 Western countries. It has steadily improved during the last decades and the number of  
5 CRC-survivors is steadily increasing [2, 3]. Hence, aspects of survivorship care become  
6 more important. CRC survivors often deal with health-related impairments and social  
7 issues as a result of the cancer disease and the intensive cancer treatment. When  
8 compared to the general population, CRC survivors are more likely to report fatigue and  
9 bowel disorders [4, 5]. Apart from physical impairments, survivors might experience  
10 depressive symptoms, fear of recurrence or financial strain [6-8]. In particular, fecal  
11 incontinence or ostomy-related problems can lead to restriction in patients' social life  
12 [9-11]. Furthermore, the typical late onset of the disease goes along with the risk of pre-  
13 existing health conditions [12]. Both, older age and multimorbidity have been shown to  
14 slow down recovery after primary treatment and increase the risk of losing  
15 independence in cancer patients [13, 14].

16 Considering the short- and long-term consequences of CRC and its treatment, the  
17 implementation of effective cancer rehabilitation in the continuum of care may be of  
18 great importance. Indication, utilization and treatment setting of rehabilitation therapy  
19 in CRC patients vary strongly between health care systems. Rehabilitative treatment is  
20 predominantly offered in outpatient settings in many countries [15, 16]. In contrast,  
21 Germany, Austria and Switzerland provide inpatient care as standard treatment and as  
22 many as 50% of incident CRC cases undergo inpatient rehabilitation therapy [17-20].  
23 These inpatient rehabilitation facilities provide multidisciplinary treatment programs  
24 that focus on individual needs and include psychosocial support, patient education,  
25 stoma care, dietetic treatment, occupational therapy, physical therapy / exercise. The

1 inpatient setting is cost-intensive but may serve as a good basis for a patient-centred and  
2 comprehensive treatment by rehabilitation professionals.

3           Previous studies have evaluated cancer inpatient rehabilitation and health  
4 outcomes but did not distinguish between cancer types [21-24] or focused on patients  
5 with cancer types other than CRC, such as CNS-tumour [22, 25], breast [26-28] and  
6 lung cancer [29, 30]. Findings from these studies might therefore not be generalizable to  
7 CRC patients, since they differ from other cancer patients in terms of survival [1],  
8 functional impairments [31, 32] as well as benefits of rehabilitative treatment [33-35].  
9 The outlined differences thus support the need for cancer site-specific research. The  
10 primary aim of the present work is to summarize and evaluate evidence on changes in  
11 health-related outcomes among CRC patients undergoing inpatient rehabilitation  
12 therapy. In addition, we aim to summarize and evaluate evidence on effectiveness of  
13 inpatient rehabilitation therapy on health-related outcomes.

14

## 1 **Materials and Methods**

### 2 *Data sources and literature search*

3 The literature search was carried out up to October 2019 using Pubmed and Web of  
4 Science databases to find articles on changes in health-related outcomes among CRC  
5 patients undergoing multidisciplinary inpatient rehabilitation programs or effects of  
6 multidisciplinary inpatient rehabilitation programs in CRC patients. Furthermore, we  
7 screened the references of the eligible articles. A non-systematic and non-cancer-site-  
8 specific pre-search was conducted beforehand to find and evaluate relevant search  
9 terms. The following combination of search terms was applied in the final systematic  
10 search: (oncology, oncological, oncologic, cancer, malignancy, malignant, neoplasms,  
11 neoplasia, neoplasm, carcinoma, tumour, tumours, tumor OR tumors) AND (colorectal,  
12 colon, colonic, rectum, rectal, gastrointestinal, digestive, intestines, intestine, intestinal,  
13 bowel OR bowels) AND reha\* (see Appendix 1: search strategies).

### 14 *Study selection*

15 We included observational studies that assessed health-related outcomes in rehabilitants  
16 at two or more time points. We included interventional studies, which investigated the  
17 effect of multidisciplinary inpatient rehabilitation program in general or the effect of  
18 one treatment method within the program. In order to fulfil the inclusion criteria  
19 “multidisciplinary rehabilitation program”, the study needed to be conducted in an  
20 inpatient rehabilitation facility or the investigated intervention consisted of more than  
21 one therapy form (nutritional support, psychological support, stoma care, patient  
22 education, occupational therapy, physical therapy / exercise) provided by several  
23 professionals. We only considered studies that were conducted in an inpatient setting.  
24 Studies, which also included patients with other diseases or cancer sites, were selected,

1 if results were presented separately for CRC patients or if at least 70 % of the study  
2 population or respective subgroup was diagnosed with CRC. In addition, we included  
3 studies without cancer site-specific analysis if no interaction effect between cancer site  
4 and treatment effect / change in health-related outcomes was found. We selected peer-  
5 reviewed English and German articles. Articles primarily covering palliative or  
6 prehabilitative treatment (i.e., treatment before surgery to enhance recovery) as well as  
7 poster abstracts, editorials, case reports, reviews and commentaries were not considered.  
8 The selection process was structured in an initial abstract-/title screening and a  
9 following full-text assessment. Both the literature search and study selection were  
10 conducted by the first author (SS).

#### 11 ***Data extraction***

12 Three researchers (SS, LJ/DB), two researchers for each included article, independently  
13 extracted relevant data into a standardized form. Information on first author, year of  
14 publication, country, study design, study inclusion criteria, number of CRC  
15 rehabilitants, treatment, health-related outcome, instruments used, time of assessments,  
16 key findings and conclusions were extracted. If a study included participants with  
17 different cancer sites and site-specific results were provided, only data based on CRC  
18 participants were extracted. If no site-specific results were given but at least 70 % of the  
19 study population / respective subgroup was diagnosed with CRC or no interaction  
20 between cancer site and treatment effect was found, we extracted data based on the  
21 whole study population / subgroup. Discrepancies in the extracted data were addressed  
22 by further review and discussion. We synthesized study findings narratively. The  
23 results of this review are presented by health-outcome or related health-outcomes for  
24 observational and interventional studies separately.



1 ***Quality assessment***

2 In order to evaluate the quality of information, we created a score from zero (strong  
3 limitations) to six (no limitations) based on the following methodological aspects:  
4 representativeness of selected participants, inclusion of comparison group, instruments  
5 used, length /completeness of follow-up and appropriateness of statistical methods. The  
6 scores are presented in Table 1 and 2 (see Appendix 2: detailed quality assessment).The  
7 rating reflected the strengths and limitations with respect to the present research  
8 objective and not necessarily the overall quality of the included study. The presence of  
9 comparison groups (i.e. no rehabilitative treatment) was obligatory to draw conclusions  
10 about effectiveness of treatment beyond changes in health-related outcomes. Only a  
11 controlled study can distinguish between improvements over time that might be likely  
12 after the completion of cancer treatment and additional improvement due to  
13 rehabilitation therapy.

14

## 1 **Results**

### 2 *Search results and study selection*

3 The electronic search identified 3604 records. Review of their title and abstracts  
4 revealed 87 potentially eligible articles that underwent full-text review. Cross-  
5 referencing and the non-systematic pre-search also identified one article each, which  
6 had not been indexed in the present search but qualified for full-text screening. Of the  
7 89 articles, ten articles (eleven studies) [31, 35-43] were considered eligible for the  
8 review. The included articles consisted of eight observational patient cohort studies and  
9 three interventional studies (one RCT, two randomized trials). **Figure 1** illustrates the  
10 selection process.

11 Twenty-four articles were excluded during full-text screening, because the  
12 respective studies were not conducted in a (multidisciplinary) rehabilitation therapy  
13 setting. In 28 articles, rehabilitative treatment took place in outpatient facilities. We also  
14 excluded 22 articles during full-text screening, that covered health-related outcomes in  
15 cancer rehabilitants but neither provided the exact number of CRC participants nor  
16 reported stratified results by cancer site. Finally, we excluded five articles, because the  
17 investigated outcomes were not of interest (e.g. assessing prevalence of health-related  
18 outcome and not its change).

### 19 *Study characteristics of observational studies*

20 Study characteristics and findings of the included observational studies are summarized  
21 in **Table 1**. The observational patient cohort studies were conducted in Germany (six  
22 studies) [31, 36-39], Austria (one study) [40] and the USA (one study) [35]. One study  
23 primarily investigated health-related changes in CRC patients [37]. Seven studies  
24 included patients with other diseases or cancer types besides CRC [31, 35, 36, 38-40].

1 No observational study included a comparison (e.g. patients not receiving rehabilitative  
2 treatment). Therefore, only changes during rehabilitative treatment but no treatment  
3 effects could be investigated. The number of included CRC rehabilitants ranged from 37  
4 to 1,732, with only two studies including more than 100 rehabilitants [35, 40]. Health-  
5 related outcomes comprised functional and physical status, fecal incontinence, QOL,  
6 anxiety and depression. The observational studies investigated health-related outcomes  
7 in retrospective or prospective cohorts of rehabilitants undergoing routine treatment. No  
8 study provided a detailed description of received treatment including therapy intensity /  
9 frequency. Five studies gave a general description of standard treatment (mainly  
10 consisting of medical care, physical therapy / exercise, occupational therapy and  
11 psychosocial support) [31, 35, 37, 38, 40]. Two studies evaluated pelvic floor exercise  
12 with or without biofeedback training as part of routine care in irradiated and non-  
13 irradiated rehabilitants with fecal incontinence [37, 38]. The duration of treatment  
14 ranged from eleven to 28 days. Health-related outcomes were assessed at admission /  
15 the beginning of treatment in all studies. Re-assessment was conducted at the end of  
16 treatment in seven studies [35-40] and four months after rehabilitation in one study [31].  
17 Additional follow-ups were conducted and respective data were provided for four  
18 studies [36-39].

## 19 *Study findings of observational studies*

### 20 *Functional status and level of independence*

21 Mix et al. [35] reported large improvements of the functional status from admission to  
22 discharge in CRC rehabilitants. Mean score values of the clinician-assessed Functional  
23 Independence Measure (FIM) increased by about one third of the initial values. The  
24 functional status comprised these dimensions: self-care, continence, mobility, transfers,

1 communication and cognition. Changes in FIM-total score varied significantly by  
2 cancer site. Rehabilitants with digestive cancers of whom 51.8 % had CRC showed the  
3 greatest functional gain during rehabilitation when compared to other cancer diagnosis.  
4 About three out of four CRC patients were discharged to a community setting.

#### 5 *Physical status*

6 Biskup and colleagues investigated the patient-perceived impairment due to physical  
7 symptoms by the Zerssen's list of somatic complaints (“Beschwerdeliste”) in two  
8 separate samples of rehabilitants (BMFT-/ARGE-study) [36]. Compared to the time of  
9 admission, participants of the BMFT-study had significantly lower levels of impairment  
10 at discharge but higher levels six months after rehabilitation. In contrast, no significant  
11 change in level of impairment was observed during or after rehabilitation therapy in the  
12 ARGE-study. Only participants diagnosed with cancer stage III or IV presented reduced  
13 impairment at the end of the therapy, but the improvements waned over time.

#### 14 *Fecal continence*

15 Allgayer and colleagues evaluated pelvic floor exercise as one integral part of routine  
16 rehabilitation therapy in two separate studies. Irradiated and non-irradiated CRC  
17 patients having fecal incontinence received pelvic floor exercise with biofeedback [37]  
18 or without/without biofeedback training [38]. The analysis did, however, not distinguish  
19 between biofeedback use [38]. Irradiated and non-irradiated patients presented clinically  
20 relevant and significant improvements in both studies at the end of inpatient treatment,  
21 but the improvement declined one year after rehabilitation in both groups and did not  
22 reach significance when compared to baseline levels in one study [38]. One study  
23 reported short- and long-term treatment failure: severe incontinence was present in nine  
24 participants (n=95) at discharge and in 19 (n=71) one year after rehabilitation, of whom

1 14 showed no treatment failure at discharge [37]. Both studies suggested a clinically  
2 relevant short-term treatment effect but no or non-clinically relevant long-term effect.

### 3 *Anxiety and Depression*

4 Two studies investigated levels of anxiety and depression but findings were not  
5 conclusive. Klocker et al. [40] reported decreased levels of anxiety and depression from  
6 admission to discharge. Lamprecht and colleagues [39] used the same screening  
7 instrument (Hospital Anxiety and Depression Scale) but evaluated the number of  
8 positive screened individuals rather than score values in total. The proportion of  
9 participants with elevated score levels for depression decreased from 15% at admission  
10 to 8% at discharge but increased to 10% three months after rehabilitation. Regarding  
11 elevated score levels for anxiety, the proportion remained unchanged from admission to  
12 discharge (8 %) but decreased three months after rehabilitation (5%). However, ,  
13 statistical test revealed no differences in the proportion of positive screened individuals  
14 for the subscales depression and anxiety over time, in contrast to findings among breast  
15 and prostate cancer patients.

### 16 *Health-related quality of life*

17 Three studies assessed changes in quality of life (QOL) during and after rehabilitation  
18 [31, 39, 40]. Overall, the studies showed positive changes in various dimensions of  
19 QOL with the exception of financial stress, which rather seemed to increase after  
20 rehabilitation. Singer et al. [31] assessed QOL by the cancer-specific instrument by the  
21 European Organisation for Research and Treatment (EORTC-QLQ-C30) at admission  
22 and four months after rehabilitation in cancer patients older than 69 years. They  
23 reported clinically relevant and positive changes (>/< 10 points) in global QOL as well  
24 as in the functional scales: physical, role, emotional, social and in the symptom scales:

1 fatigue, dyspnoea, nausea/vomiting, pain, appetite loss. Lamprecht et al. [39] assessed  
2 changes in QOL with the same instrument during rehabilitation and three months after  
3 rehabilitation. All QOL scales improved during rehabilitation among colon cancer  
4 patients except financial problems. Smaller improvements or slight deteriorations were  
5 seen three months after rehabilitation, but latter did not reach initial values. Age and  
6 time-since-diagnosis adjusted analyses revealed largest and significant improvement for  
7 global QOL and fatigue during rehabilitation and largest improvement in physical  
8 functioning in the period after rehabilitation. Klocker and colleagues [40] assessed QOL  
9 by the EuroQoL-EQ-5D-VAS. Rehabilitants rated their overall health status higher at  
10 the end of treatment than at the beginning (mean score 71.5 vs. 59.4 /100, no  
11 significance test provided).

#### 12 *Changes in health-related outcomes in the course of time*

13 Among the four studies that assessed health-related outcomes (physical status, fecal  
14 continence) at the end of treatment and six months or more after rehabilitation [36-38],  
15 three studies noted an improvement in the respective outcomes during rehabilitation and  
16 slight or strong deterioration in the period after rehabilitation among CRC patients.  
17 Klocker et al. [40] did not provide cancer site-specific follow-up data of the whole study  
18 population but reported similar courses (i.e. an improvement during rehabilitation  
19 followed by deteriorations at six and twelve months after rehabilitation) for the  
20 outcomes health status, anxiety and depression in a subset of long-term followed-up  
21 cancer patients.

1 ***Study characteristics of the interventional studies***

2 **Table 2** provides an overview of the characteristics and findings of the included  
3 interventional studies. The trials were conducted in Germany (two studies) [41, 42] and  
4 Denmark (one study) [43]. The number of included CRC patients ranged from 23 to  
5 124. The only RCT [43] we were able to identify was also the only included study that  
6 involved a comparison group without treatment allocation in order to investigate  
7 effectiveness of treatment. Ross et al. investigated the effect of a six-day inpatient  
8 rehabilitation course on distress 12 months after the course [43]. Further outcomes of  
9 the study are published elsewhere [44, 45] but relevant information (CRC-specific  
10 results / information on interaction between cancer site and effect) was not provided. .  
11 The two remaining randomized trials investigated the effect of different aerobic exercise  
12 intensities on immune response [41] and on oxidative stress [42] respectively after two  
13 weeks of intervention in CRC patients undergoing routine rehabilitative care.

14 **Study findings of the interventional studies**

15 **Psychologic distress**

16 Ross et al. [43] investigated the effect of a multidimensional rehabilitation  
17 program on distress using the Total Mood Disturbance Score, which was derived  
18 from the Profile-of-Mood-States Short-Form. No effect on distress 12 months  
19 after treatment was observed. Changes in distress from before to one and six  
20 months after treatment were published elsewhere [45], but the reported results  
21 were adjusted for cancer site and did not necessarily reflect changes in  
22 participants with CRC. The control group reported greater decrease in distress one  
23 and six months after treatment in comparison to the intervention group, which  
24 reported small and marginal decrease.

25

1 Biomarkers: immune response and oxidative stress

2 Results from two studies suggest that the intensity of endurance training during

3 rehabilitative treatment could influence immune response [41] and the level of oxidative

4 stress [42]. Both studies compared two-week aerobic exercise with lower (30–40 % x

5 maximal exercise capacity) and higher intensity (50–60 % / 55–65 %). A significant

6 reduction in oxidative stress levels measured by urinary 8-Oxo-2'-deoxyguanosine was

7 observed from before treatment to after treatment in the lower exercise intensity group

8 in comparison to no significant reduction in the higher intensity group [42]. A

9 significant decrease in anti-inflammatory cytokines (Lipopolysaccharide-stimulated

10 interleukin-1 receptor antagonist) was observed in the higher intensity group in

11 comparison to no significant change in the lower intensity group [41]. The potential

12 benefit for both outcomes with respect to infection rate, anti-tumour response and

13 survival is unknown hitherto as pointed out by the authors.



## 1 **Discussion**

2 We identified eleven studies, three interventional studies and eight observational patient  
3 cohort studies, which investigated changes in health-related outcomes in CRC  
4 rehabilitants. As anticipated, evidence is very limited and essentially restricted to  
5 changes during or after inpatient rehabilitation therapy, since only one study included a  
6 comparison group without rehabilitative treatment [43]. Besides the findings of the  
7 respective study, one cannot draw explicit conclusion about effectiveness of inpatient  
8 rehabilitation therapy. The lack of a control group does not allow distinguishing any  
9 improvements that might have occurred with or without rehabilitation therapy. In this  
10 case, descriptive observational data from cohort studies were essentially the only  
11 evidence we could look at regarding potential rehabilitation effects, even though results  
12 have to be interpreted with caution.

### 13 *Summary of study findings and comparison to previous studies*

14 The relevant studies covered a wide range of health outcomes (e.g. functional status,  
15 fecal incontinence, mental health, QOL, oxidative stress and immune response).  
16 Findings from the included studies suggest that rehabilitants show clinically relevant  
17 improvement in particular in physical functions and several dimensions of QOL as well  
18 as overall health status at the end of rehabilitation or shortly after rehabilitative  
19 treatment. A need for rehabilitative care and an improvement in the QOL after  
20 rehabilitation was also observed in older colon cancer patients [31]. The findings of  
21 positive changes in physical health are consistent with findings from other studies that  
22 investigated somatic status [33, 46], functional status [47] and QOL [48] in rehabilitants  
23 with various cancers. The two included RT investigated short-term physiological  
24 adaption following different aerobic exercise intensities [41, 42]. Lower exercise  
25 intensity was linked to a reduction in oxidative stress [42], whereas a decrease in anti-

1 inflammatory cytokines was linked to higher exercise intensity [41]. The potential  
2 benefit of certain exercise intensity with respect to infection rate, tumour recurrence and  
3 survival is not known and requires further research. The American College of Sports  
4 Medicine recommends moderate to vigorous exercise intensities but also point out the  
5 limited evidence behind the given recommendations for CRC patients and survivors  
6 [49].

7         The picture is less clear with regard to changes in psychological strain. One  
8 single study was able to investigate effects of inpatient rehabilitation treatment due to  
9 the controlled design and reported no effect on distress 12 months after treatment [43].  
10 One possible explanation for the negative findings might be the short and non-cancer-  
11 site-specific rehabilitation program. In comparison to the other included studies, the  
12 multidisciplinary program consisted of a short six-day workshop for breast, prostate and  
13 colorectal cancer patients that mainly included peer-group sessions and lectures rather  
14 than individual tailored three/four-week treatments involving frequent one-to-one  
15 therapy sessions with rehabilitation professionals [45]. The only randomized study was  
16 also limited by ineffective randomization with respect to initial distress and lack of  
17 follow-up of many non-receivers (intervention group), who tended to be less distressed  
18 at baseline. Reported changes from baseline to one and six months after the intervention  
19 were adjusted by cancer-site [45] and score changes from baseline to 12 months after  
20 the intervention were not provided [43]. Therefore, we could not draw direct  
21 comparison to the findings of the included observational studies. Two other studies  
22 came to different conclusions regarding the endpoints anxiety and depression. One  
23 study reported a decrease of anxiety and depression level during rehabilitation [40] and  
24 the other study did not observed a decrease over time [39]. Based on the limited  
25 evidence, no conclusion can be made. However, a reduction of anxiety and depression

1 [46] as well as psychosocial stress levels [48] during inpatient rehabilitation among  
2 cancer patients has been reported previously. With regard to positive changes on the  
3 physical level, CRC patients appeared to benefit most from rehabilitation therapy when  
4 compared to other cancer patients [33, 35, 39]. This aspect could be related to stronger  
5 physical impairments among CRC at admission in comparison to breast or prostate  
6 cancer patients [31, 39]. In contrast, CRC patients may experience a greater  
7 psychological burden after rehabilitation. A study by Mehnert et al., for example,  
8 identified CRC, hematologic and skin cancer as one predictor for persistent fear of  
9 recurrence after inpatient rehabilitation therapy in cancer patients. Higher levels of fear  
10 of recurrence in CRC patients might be partially related to general poorer prognosis  
11 than for example in breast or prostate cancer patients [34]. In addition to psychological  
12 strain, cancer patients are under risk experiencing financial strain, which seems to  
13 remain or even increase after rehabilitation as observed in two included studies [31,39].  
14 The findings might reflect accumulating out-of-pocket payments for medical care and /  
15 or ongoing temporary or permanent disability in younger working patients.

16         The included observational studies, which followed-up participants six months  
17 or longer, indicate that the improved health status after rehabilitation may decrease over  
18 time. A recurrent increase in symptoms after the rehabilitation stay has also been  
19 described in other studies [33, 34]. Cancer patients might struggle with applying  
20 recommendations and learned coping strategies in daily life. Furthermore, there is no  
21 systematic and comprehensive after-care provision by local rehabilitation professionals  
22 in order to consolidate treatment success and respond to emerging health conditions.

### 23 ***Methodological quality of included studies and implication for future studies***

24 The methodological quality of the included studies was fair. However, there are several  
25 limitations with regard to the answer to our research questions. First, except in three

1 studies [35, 40, 43], the numbers of included CRC patients were low (< 100). The small  
2 sample size likely hindered further stratification by potentially relevant factors such as  
3 cancer stage, time-since-diagnosis, completeness of treatment and age for most analysis.  
4 In order to investigate changes in physical and psychological health as well as potential  
5 determinants of treatment success with adequate statistical power, higher numbers of  
6 CRC patients would be needed. Disclosure of such determinants would be essential for  
7 identifying individuals, who have rehabilitative needs but show no or no long-term  
8 improvement despite standard rehabilitative measures. Due to the different scope of  
9 some studies, authors provided cancer-specific descriptive values of the assessed health  
10 outcomes but no information about inferential statistics [31, 35, 39, 40]. Among those  
11 that performed statistical testing, significance levels were often not reached likely due to  
12 limited statistical power. Second, the study populations of many studies were restricted  
13 to patients below 70 or 75 years [37-39, 41, 42]. Except in two studies [31, 35], we  
14 observed a low mean age (57-62 years) or median age (54-63) of the included  
15 participants, given that the median age at the time of diagnosis for CRC is about 70 in  
16 developed countries [50]. Thus, evidence is limited for the large proportion of older  
17 CRC patients. Third, length of observational periods varied from treatment period only  
18 [35, 41, 42] to three to 12 months after rehabilitation. Only studies with long  
19 observation periods beyond the time of discharge were able to evaluate the potential  
20 benefit of inpatient rehabilitation in everyday environment. Eventually only one study  
21 included a comparison group (non-rehabilitants). Due to the lack of control groups, one  
22 cannot draw explicit conclusion about effectiveness of treatment. An initial  
23 improvement in health status after the completion of active treatment seems likely with  
24 or without rehabilitative treatment. In order to establish evidence on the effectiveness of  
25 inpatient rehabilitation, RCTs would be highly desirable. However, in countries where

1 inpatient rehabilitation is an established integral part of routine care, conducting studies  
2 with random treatment allocation would be difficult to conduct. Wait-list control groups  
3 and matched-pair-analysis, such as propensity score analysis, might be considered as  
4 possible alternative approaches to limit potential confounding as far as possible.  
5 Interventional studies with active controls or observational cohort studies could also  
6 enable some conclusion on the effectiveness of specific elements of rehabilitation  
7 therapy within patient cohorts.

### 8 ***Strengths and limitation of this review***

9 Despite a comprehensive literature search in two established databases and intensive  
10 cross-referencing, we cannot rule out having missed relevant articles. Only one  
11 researcher (SS) performed the study selection, but all authors were involved in and  
12 evaluated the process. The CRC-specific search might have excluded studies that  
13 provided subgroup analyses for patients with specific cancers such as CRC, which were  
14 not mentioned in the abstract. Due to the small number of relevant peer-reviewed  
15 publications, we also included articles on CRC patients that provided descriptive results  
16 of health-related changes only and no information about statistical testing, which limits  
17 conclusions from the results. Since most studies were conducted in Germany, findings  
18 can best be generalized to the German rehabilitation setting. We anticipated this aspect  
19 given the high utilization of inpatient cancer rehabilitation in Germany among CRC  
20 patients [17-19] in comparison to predominant outpatient settings or low utilization  
21 rates of rehabilitative treatment in other health-care systems [15, 16]. Although we  
22 included studies that reported null results, we cannot exclude the possibility of a general  
23 publication bias.

1 ***Conclusion***

2 To our knowledge, our study is the first to summarize the available evidence on changes  
3 in health-related outcomes following inpatient rehabilitation among CRC patients in a  
4 systematic review. Overall, evidence is very limited due to the small number and  
5 methodological limitations of available studies. The uncontrolled design of most  
6 studies, first and foremost did not allow us to draw conclusions about treatment effects.  
7 Available evidence is mostly restricted to changes of certain health aspects during  
8 inpatient rehabilitation therapy. Improvements during inpatient rehabilitation have been  
9 reported in physical health, independence and QOL among CRC patients. However,  
10 where assessed, such improvements did often not persist after discharge from inpatient  
11 rehabilitation, suggesting the need for rehabilitative measures that promote health and  
12 social participation in the longer run. There are research gaps concerning psychologic  
13 strain and colon cancer-specific health impairments, such as nutrition, stool regulation,  
14 fatigue and chemotherapy-induced peripheral neuropathy. Cancer and CRC-specific  
15 instruments could provide a better assessment of rehabilitative needs and benefits in  
16 CRC patients in future studies. Little is known whether inpatient rehabilitation might  
17 enhance adherence and completion of adjuvant cancer treatment and if the timing of  
18 rehabilitation before or after adjuvant treatment is preferable with respect to side effects,  
19 completion of adjuvant treatment and survival. Further large representative studies  
20 including control groups and long-term follow-up are needed to evaluate the  
21 effectiveness of inpatient rehabilitation. Moreover, the investigation of determinants of  
22 treatment success and failure is essential for developing targeted treatment strategies for  
23 CRC survivors in the future.

24 \*\*\*

1 Table 1. Characteristics of included observational studies, relevant findings among CRC  
2 rehabilitants and results of the quality assessment

3 Table 2. Characteristics of included interventional studies, relevant findings among  
4 CRC patients and results of the quality assessment

5 Figure 1. PRISMA Flow diagram of literature search and study selection process

6 \*\*\*

7 Supplemental materials

8 Appendix 1: Search strategies

9 Appendix 2: Quality assessment of the included observational and interventional studies

10 Appendix 3: PRISMA checklist

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