

REVIEW



Changes in health-related outcomes among colorectal cancer patients undergoing inpatient rehabilitation therapy: a systematic review of observational and interventional studies

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ABSTRACT

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

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

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

Conclusion: The scientific evidence level was very limited. Due to the lack of a comparison group in most studies, we were only able to evaluate changes during/after inpatient rehabilitation therapy but not the effectiveness of treatment. However, study findings suggest that physical health and functional independence improve during inpatient rehabilitation, but improvements wane over time. Further large representative studies, in particular RCTs with long-term follow-up, are essential to evaluate the effectiveness of inpatient rehabilitation and identify determinants of treatment success.

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Introduction

Colorectal cancer (CRC) is the third most frequent cancer worldwide with an estimated 1.8 million new cases in 2018 [1]. The current 5-year relative survival is about 63% in Western countries. It has steadily improved during the last decades and the number of CRC-survivors is steadily increasing [2,3]. Hence, aspects of survivorship care become more important. CRC survivors often deal with health-related impairments and social issues as a result of the cancer disease and the intensive cancer treatment. When compared to the general population, CRC survivors are more likely to report fatigue and bowel disorders [4,5]. Apart from physical impairments, survivors might experience depressive symptoms, fear of recurrence, or financial strain [6–8]. In particular,

fecal incontinence or ostomy-related problems can lead to restrictions in patients' social life [9–11]. Furthermore, the typical late onset of the disease goes along with the risk of preexisting health conditions [12]. Both, older age and multimorbidity have been shown to slow down recovery after primary treatment and increase the risk of losing independence in cancer patients [13,14].

Considering the short- and long-term consequences of CRC and its treatment, the implementation of effective cancer rehabilitation in the continuum of care may be of great importance. Indication, utilization, and treatment setting of rehabilitation therapy in CRC patients vary strongly between health care systems. Rehabilitative treatment is predominantly offered in outpatient settings in many countries [15,16].

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In contrast, Germany, Austria, and Switzerland provide inpatient care as a standard treatment and as many as 50% of incident CRC cases undergo inpatient rehabilitation therapy [17–20]. These inpatient rehabilitation facilities provide multidisciplinary treatment programs that focus on individual needs and include psychosocial support, patient education, stoma care, dietetic treatment, occupational therapy, physical therapy/exercise. The inpatient setting is cost-intensive but may serve as a good basis for a patient-centered and comprehensive treatment by rehabilitation professionals.

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

Material and methods

Data sources and literature search

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

Study selection

We included observational studies that assessed health-related outcomes in rehabilitants at two or more time points. We included interventional studies, which investigated the effect of a multidisciplinary inpatient rehabilitation program in general or the effect of one treatment method within the program. In order to fulfill the inclusion criteria ‘multidisciplinary rehabilitation program’, the study needed to be conducted in an inpatient rehabilitation facility or the

investigated intervention consisted of more than one therapy form (nutritional support, psychological support, stoma care, patient education, occupational therapy, physical therapy/exercise) provided by several professionals. We only considered studies that were conducted in an inpatient setting. Studies, which also included patients with other diseases or cancer sites, were selected, if results were presented separately for CRC patients or if at least 70% of the study population or respective subgroup was diagnosed with CRC. In addition, we included studies without cancer site-specific analysis if no interaction effect between cancer site and treatment effect/change in health-related outcomes was found. We selected peer-reviewed English and German articles. Articles primarily covering palliative or prehabilitative treatment (i.e., treatment before surgery to enhance recovery) as well as poster abstracts, editorials, case reports, reviews, and commentaries were not considered. The selection process was structured in an initial abstract-/title screening and a following full-text assessment. Both the literature search and study selection were conducted by the first author (SS).

Data extraction

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

Quality assessment

In order to evaluate the quality of information, we created a score from zero (strong limitations) to six (no limitations) based on the following methodological aspects: representativeness of selected participants, inclusion of comparison group, instruments used, length/completeness of follow-up and appropriateness of statistical methods. The scores are presented in [Tables 1 and 2](#) (see [Supplementary Appendix 2: detailed quality assessment](#)). The rating reflected the strengths and limitations with respect to the present research objective and not necessarily the overall quality of the included study. The presence of comparison groups (i.e., no rehabilitative treatment) was obligatory to draw conclusions about the effectiveness of the treatment beyond

changes in health-related outcomes. Only a controlled study can distinguish between improvements over time that might be likely after the completion of cancer treatment and additional improvement due to rehabilitation therapy.

Results

Search results and study selection

The electronic search identified 3604 records. A review of their title and abstracts revealed 87 potentially eligible articles that underwent full-text review. Cross-referencing and the nonsystematic pre-search also identified one article each, which had not been indexed in the present search but qualified for full-text screening. Of the 89 articles, 10 articles (11 studies) [31,35–43] were considered eligible for the review. The included articles consisted of eight observational patient cohort studies and three interventional studies (one RCT, two randomized trials). Figure 1 illustrates the selection process.

Twenty-four articles were excluded during full-text screening because the respective studies were not conducted in a (multidisciplinary) rehabilitation therapy setting. In 28 articles, the rehabilitative treatment took place in outpatient facilities. We also excluded 22 articles during full-text screening, that covered health-related outcomes in cancer rehabilitants but

neither provided the exact number of CRC participants nor reported stratified results by cancer site. Finally, we excluded five articles, because the investigated outcomes were not of interest (e.g., assessing the prevalence of a health-related outcome and not its change).

Study characteristics of observational studies

Study characteristics and findings of the included observational studies are summarized in Table 1. The observational patient cohort studies were conducted in Germany (six studies) [31,36–39], Austria (one study) [40], and the USA (one study) [35]. One study primarily investigated health-related changes in CRC patients [37]. Seven studies included patients with other diseases or cancer types besides CRC [31,35,36,38–40]. No observational study included a comparison (e.g., patients not receiving rehabilitative treatment). Therefore, only changes during rehabilitative treatment but no treatment effects could be investigated. The number of included CRC rehabilitants ranged from 37 to 1732, with only two studies including more than 100 rehabilitants [35,40]. Health-related outcomes comprised functional and physical status, fecal incontinence, QOL, anxiety, and depression. The observational studies investigated health-related outcomes in retrospective or prospective cohorts of rehabilitants

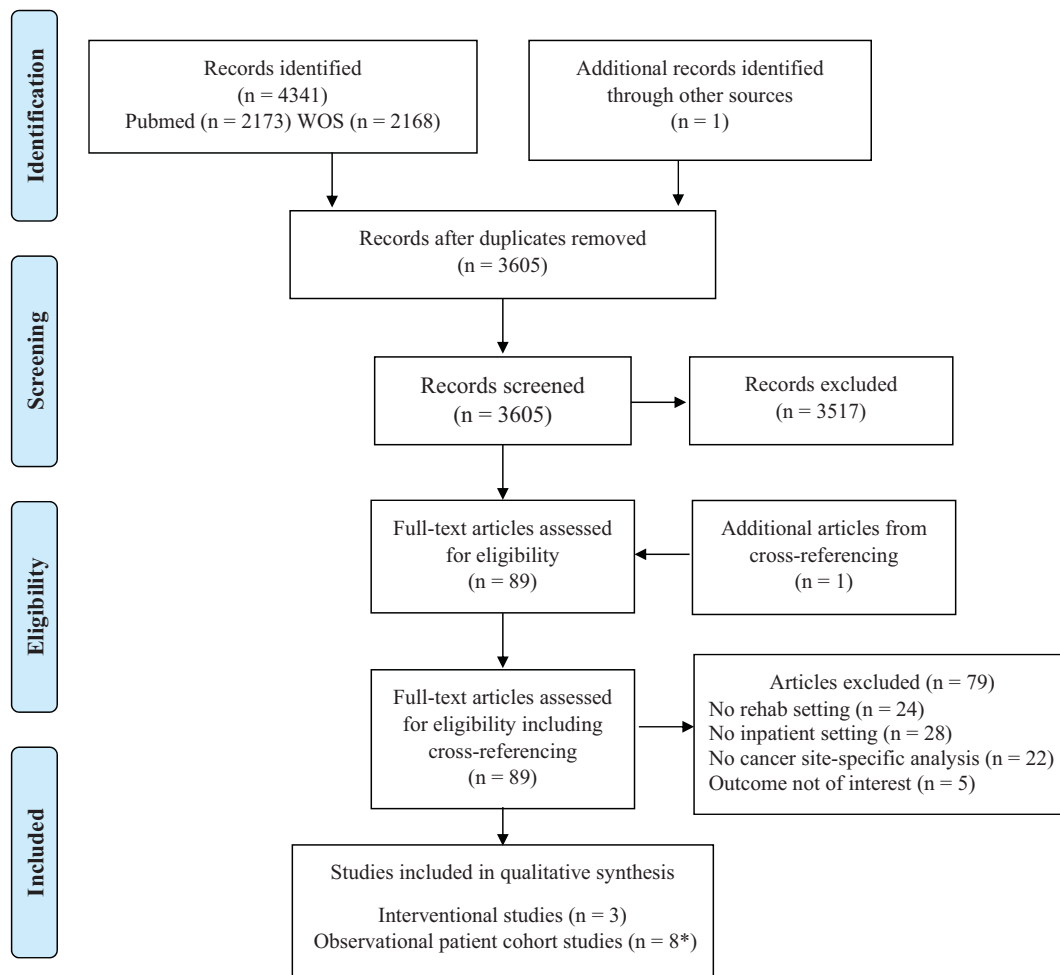


Figure 1. PRISMA flow diagram of literature search and study selection process. *The article by Biskup et al. [36] covers two individual studies.

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

First author Year Country	Study design Comparison group never included	Included CRC patients ^a	Therapy / duration (days)	Relevant outcomes	Re-assessment ^b			Relevant findings /quality assessment (total score)
					Instruments used	Short-term	Long-term	
Mix 1977 USA [35]	Retrospective patient cohort	1732	Routine inpatient rehab. therapy ~11.3 ^c	Functional status	FIM (Functional Independence Measure)	✓		- Functional gain was observed at discharge. - Patients with digestive cancers had the largest functional gain. TS 3 Δ moderate limitations
Biskup 1994 Germany [36]	a. Prospective patient cohort	40	Routine inpatient rehab. therapy 28	Physical status	Beschwerdenliste B-L (Zerssen's list of somatic complaints)	✓	✓	- Significant improvement in physical status during rehabilitation. - Increase of impairments beyond the initial level 6 months after rehabilitation. TS 2 Δ strong limitations
	b. Prospective patient cohort	83	Routine inpatient rehab. therapy ^d	Physical status	Beschwerdenliste B-L (Zerssen's list of somatic complaints)	✓	✓	No improvements in physical status during or 3 and 6 months after rehabilitation. TS 3 Δ moderate limitations
Allgayer 2012 Germany [38]	Prospective patient cohort ^e	67 ^f (rectal cancer)	Routine inpatient rehab. therapy including intensive pelvic floor exercise with/without biofeedback 21–28	Fecal Incontinence	MCIS (Modified Cleveland Incontinence Score)	✓	✓	- No difference in levels of fecal incontinence between non- and irradiated-rehabilitants at admission. - Significant reduction in levels of fecal incontinence in both groups during rehabilitation. - Deteriorations 1 year after rehabilitation up to initial values. TS 4 Δ moderate limitations
	Prospective patient cohort	95	Routine inpatient rehab. therapy including intensive pelvic floor exercise with biofeedback 21	Fecal Incontinence	MCIS (Modified Cleveland Incontinence Score)	✓	✓	- Irradiation was significantly associated with higher levels of fecal incontinence at the start of rehabilitation. - Significant reduction in levels of fecal incontinence during and 1 year after rehabilitation compared to admission in both groups. - Slight increase in levels of fecal incontinence 1 year after rehabilitation. - Treatment failure during and 1 year after rehabilitation: in 9 (9/95) and 19 (19/71)
Allgayer 2005 Germany [37]	Prospective patient cohort			Anal pressure sensation/pain spincter length	Rectal manometry Balloon instillation Rectal endoscopy	✓	(✓) ^g	No significant change in anal pressure or sensation / pain during rehabilitation. TS 4 Δ moderate limitations

(continued)

Table 1. Continued.

First author Year Country	Study design Comparison group never included	Inclusion criteria	Included CRC patients ^a	Therapy / duration (days)	Relevant outcomes	Instruments used	Re-assessment ^b		Relevant findings (quality assessment (total score))
							Short-term	Long-term	
Klocker 2018 Austria [40]	Prospective patient cohort	• Cancer diagnosis • Returned questionnaire at discharge	291	Routine inpatient rehab. therapy 21	QOL (health status)	EuroQoL-EQ-5D-VAS (EuroQoL five-dimensional Questionnaire) HADS (Hospital Anxiety and Depression Scale)	✓	(✓) ^h	• QOL improved during rehabilitation.
							✓	(✓) ^h	• Levels of anxiety and depression decreased during rehabilitation. TS 2 Δ strong limitations
Lamprecht 2017 Germany [39]	Prospective patient cohort	• Breast, prostate, colon cancer • Stage I–III • Age 18–75 years • No tumor recurrence • First rehabilitation program	37	Routine inpatient rehab. therapy ^d	QOL	EORTC-QLQ-C30 ⁱ (EORTC Core Quality of Life Questionnaire)	✓	✓	• QOL improved during rehabilitation (except financial problems) with greatest and significant improvement in global QOL and fatigue. • Smaller improvements or deteriorations were reported 3 months after rehabilitation. Largest and significant improvements in physical functioning.
							✓	✓	• No significant change in number of positive screened individuals for anxiety and depression in the course of time TS 4 Δ moderate limitations
Singer 2009 Germany [31]	Prospective patient cohort	• Cancer diagnosis • Age >69 years • Completed or immediately preceding anti-tumor therapy	54 ^f	Routine inpatient rehab. therapy 21	QOL	EORTC-QLQ-C30 ⁱ (EORTC Core Quality of Life Questionnaire)	✓	✓	• Clinically relevant and positive change in global QOL and in the following functional scales 4 months after rehabilitation: physical, emotional, role and social as well as in the symptom scales: fatigue, dyspnea, nausea and vomiting, pain, appetite loss. • No or no clinically relevant change in the scales: cognitive functioning, financial problems, sleep, diarrhea and constipation TS 4 Δ moderate limitations
							✓	✓	

CRC: colorectal cancer; QOL: Quality of Life, TS: Total Score.

^aNumber of rehabilitants with CRC that were included in the analyses (first re-assessment);^bShort-term is defined as at the end of treatment or at discharge; Long-term is defined as 3 to 12 months after inpatient rehabilitation therapy;^cMean duration of treatment was 11.3 days in the group of patients with digestive cancer sites;^dInformation about duration is not provided. Standard therapy in Germany lasts for about 21–28 days;^eOriginally reported as prospective, comparative study (evaluating the predictive value of medical findings by endorectal ultrasound and real-time elastography on fecal continence);^fNumber of CRC patients at baseline. Results are not stratified by entity or disease but $\geq 70\%$ of study population or relevant subgroup are patients with CRC;^g22 patients were reexamined during a second rehabilitation clinic stay;^hOnly a subset of participants was followed-up 6 and 12 months after rehabilitation therapy. Relevant information was not reported separately for cancer entities;ⁱQuality of life core questionnaire by the European Organisation for Research and Treatment of Cancer.

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

First author Year Country	Study design	Inclusion criteria	Included CRC patients ^a	Intervention duration (days)	Relevant outcomes	Re-assessment ^b			Relevant findings/quality assessment (total score)
						Instruments used	Short-term	Long-term	
Ross 2015 Denmark [43]	RCT	- Breast, prostate, CRC - Low and high risk cancer - Time since diagnosis ≤ 2 years - Completed primary treatment - Life expectancy ≥ 5 months	124 ^c Intervention arm: 54 Controls: 70	Multi-focus psychosocial empowerment intervention Controls: usual clinical care 6	Distress	TMD (Total mood Disturbance score derived from the Profile of mood short Form)	(✓) ^d	✓	No association between changes in distress and group assignment, even when stratified by age, education and cancer site. TS 5 Δ minor limitations
Allgayer 2008 Germany [42]	RT ^e	- CRC - Stage I to III - Age ≤ 75 years - Completed anti-tumor therapy - Karnofsky index ≥ 80 - No severe comorbidities	44 Higher exercise intensity: 27 Lower exercise intensity: 17	Routine care + aerobic exercise (50–60% vs. 30–40% $\times$ max. exercise capacity) ^f 14	DNA-damage (Urinary 8-oxo-dG ^g)	Mass spectrometry	✓		Significant decrease in 8-oxo-dG excretion levels in the lower exercise intensity group. Non-significant increase in the higher exercise intensity group. TS 2 Δ strong limitations
Allgayer 2004 Germany [41]	RT	- CRC - Stage II or III - Age ≤ 65 years - Completed anti-tumor therapy - Karnofsky index ≥ 85 - No severe comorbidities	23 Higher exercise intensity: 13 Lower exercise intensity: 10	Routine care + aerobic exercise (55–65% vs. 30–40% $\times$ max. exercise capacity) ^f 14	Inflammatory cytokines and antagonist response	Blood samples under LPS-stimulation ^h	✓		LPS-stimulated interleukin-1 receptor antagonist decreased (IL-1 ra) significantly with higher exercise intensity. Possible link to pro- inflammatory response and decreased susceptibility to infection. TS 2 Δ strong limitations

CRC: colorectal cancer; RCT: randomized controlled trial; RT: randomized trial (randomization to different exercise intensity groups, no quantitative comparison between groups, only within groups).

^aNumber of rehabilitants with CRC that were included in the analyses (first re-assessment);

^bShort-term is defined as at the end of treatment or at discharge; Long-term is defined as 12 months after inpatient rehabilitation therapy;

^cResults are not provided by cancer site but statistical testing showed no interaction between treatment effect and cancer site;

^dShort-term assessment after treatment and further re-assessments have been published elsewhere [44,45] but relevant information about entity-specific outcomes is not provided for participants with CRC;

^eSwitching to the alternate exercise group was allowed after randomization;

^fType of exercise was not reported but stationary bike was used for max. exercise capacity test;

^g8-Oxo-2'-deoxyguanosine;

^hLPS Lipopolysaccharide.

undergoing routine treatment. No study provided a detailed description of received treatment including therapy intensity/frequency. Five studies gave a general description of standard treatment (mainly consisting of medical care, physical therapy/exercise, occupational therapy, and psychosocial support) [31,35,37,38,40]. Two studies evaluated pelvic floor exercise with or without biofeedback training as part of routine care in irradiated and non-irradiated rehabilitants with fecal incontinence [37,38]. The duration of treatment ranged from eleven to 28 days. Health-related outcomes were assessed at admission/the beginning of treatment in all studies. Re-assessment was conducted at the end of treatment in seven studies [35–40] and 4 months after rehabilitation in one study [31]. Additional follow-ups were conducted and respective data were provided for four studies [36–39].

Study findings of observational studies

Functional status and level of independence

Mix et al. [35] reported large improvements in the functional status from admission to discharge in CRC rehabilitants. The mean score values of the clinician-assessed Functional Independence Measure (FIM) increased by about one-third of the initial values. The functional status comprised these dimensions: self-care, continence, mobility, transfers, communication and cognition. Changes in the FIM-total score varied significantly by cancer site. Rehabilitants with digestive cancers of whom 51.8% had CRC showed the greatest functional gain during rehabilitation when compared to other cancer diagnoses. About three out of four CRC patients were discharged to a community setting.

Physical status

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

Fecal continence

Allgayer and colleagues evaluated pelvic floor exercise as one integral part of routine rehabilitation therapy in two separate studies. Irradiated and non-irradiated CRC patients having fecal incontinence received pelvic floor exercise with biofeedback [37] or without/without biofeedback training [38]. The analysis did, however, not distinguish between biofeedback use [38]. Irradiated and non-irradiated patients presented clinically relevant and significant improvements in both studies at the end of inpatient treatment, but the improvement declined 1 year after rehabilitation in both

groups and did not reach significance when compared to baseline levels in one study [38]. One study reported short- and long-term treatment failure: severe incontinence was present in nine participants (9/95) at discharge and in 19 (19/71) 1 year after rehabilitation, of whom 14 showed no treatment failure at discharge [37]. Both studies suggested a clinically relevant short-term treatment effect but no or non-clinically relevant long-term effects.

Anxiety and depression

Two studies investigated levels of anxiety and depression but findings were not conclusive. Klocker et al. [40] reported decreased levels of anxiety and depression from admission to discharge. Lamprecht and colleagues [39] used the same screening instrument (Hospital Anxiety and Depression Scale) but evaluated the number of positive screened individuals rather than score values in total. The proportion of participants with elevated score levels for depression decreased from 15% at admission to 8% at discharge but increased to 10% 3 months after rehabilitation. Regarding elevated score levels for anxiety, the proportion remained unchanged from admission to discharge (8%) but decreased 3 months after rehabilitation (5%). However, a statistical test revealed no differences in the proportion of positive screened individuals for the subscales depression and anxiety over time, in contrast to findings among breast and prostate cancer patients.

Health-related quality of life

Three studies assessed changes in quality of life (QOL) during and after rehabilitation [31,39,40]. Overall, the studies showed positive changes in various dimensions of QOL with the exception of financial stress, which rather seemed to increase after rehabilitation. Singer et al. [31] assessed QOL by the cancer-specific instrument by the European Organisation for Research and Treatment of Cancer (EORTC-QLQ-C30) at admission and 4 months after rehabilitation in cancer patients older than 69 years. They reported clinically relevant and positive changes (>10 / <10 points) in global QOL as well as in the functional scales: physical, role, emotional, social, and in the symptom scales: fatigue, dyspnea, nausea/vomiting, pain, appetite loss. Lamprecht et al. [39] assessed changes in QOL with the same instrument during rehabilitation and 3 months after rehabilitation. All QOL scales improved during rehabilitation among colon cancer patients except for financial problems. Smaller improvements or slight deteriorations were seen 3 months after rehabilitation, but the latter did not reach initial values. Age and time-since-diagnosis adjusted analyses revealed the largest and significant improvement for global QOL and fatigue during rehabilitation and the largest improvement in physical functioning in the period after rehabilitation. Klocker and colleagues [40] assessed QOL by the EuroQoL-EQ-5D-VAS. Rehabilitants rated their overall health status higher at the end of treatment than at the beginning (mean score 71.5 vs. 59.4/100, no significance test provided).

Changes in health-related outcomes in the course of time

Among the four studies that assessed health-related outcomes (physical status, fecal continence) at the end of treatment and 6 months or more after rehabilitation [36–38], three studies noted an improvement in the respective outcomes during rehabilitation and slight or strong deterioration in the period after rehabilitation among CRC patients. Klocker et al. [40] did not provide cancer site-specific follow-up data of the whole study population but reported similar courses (i.e., an improvement during rehabilitation followed by deteriorations at 6 and 12 months after rehabilitation) for the outcomes health status, anxiety, and depression in a subset of long-term followed-up cancer patients.

Study characteristics of the interventional studies

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

Study findings of the interventional studies

Psychologic distress

Ross et al. [43] investigated the effect of a multidimensional rehabilitation program on distress using the Total Mood Disturbance Score, which was derived from the Profile-of-Mood-States Short-Form. No effect on distress 12 months after treatment was observed. Changes in distress from before to 1 and 6 months after treatment were published elsewhere [45] but the reported results were adjusted for cancer site and did not necessarily reflect changes in participants with CRC. The control group reported a greater decrease in distress 1 and 6 months after treatment in comparison to the intervention group, which reported small and marginal decreases.

Biomarkers: immune response and oxidative stress

Results from two studies suggest that the intensity of endurance training during rehabilitative treatment could influence immune response [41] and the level of oxidative stress [42]. Both studies compared 2-week aerobic exercise with lower (30–40% × maximal exercise capacity) and higher intensity

(50–60%/55–65%). A significant reduction in oxidative stress levels measured by urinary 8-Oxo-2'-deoxyguanosine was observed from before treatment to after treatment in the lower exercise intensity group in comparison to no significant reduction in the higher-intensity group [42]. A significant decrease in anti-inflammatory cytokines (Lipopolysaccharide-stimulated interleukin-1 receptor antagonist) was observed in the higher-intensity group in comparison to no significant change in the lower-intensity group [41]. The potential benefit for both outcomes, with respect to infection rate, anti-tumor response, and survival, is unknown hitherto as pointed out by the authors.

Discussion

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

Summary of study findings and comparison to previous studies

The relevant studies covered a wide range of health outcomes (e.g., functional status, fecal incontinence, mental health, QOL, oxidative stress, and immune response). Findings from the included studies suggest that rehabilitants show clinically relevant improvement in particular in physical functions and several dimensions of QOL as well as overall health status at the end of rehabilitation or shortly after rehabilitative treatment. A need for rehabilitative care and an improvement in the QOL after rehabilitation was also observed in older colon cancer patients [31]. The findings of positive changes in physical health are consistent with findings from other studies that investigated somatic status [33,46], functional status [47], and QOL [48] in rehabilitants with various cancers. The two included RT investigated short-term physiological adaption following different aerobic exercise intensities [41,42]. Lower exercise intensity was linked to a reduction in oxidative stress [42], whereas a decrease in anti-inflammatory cytokines was linked to higher exercise intensity [41]. The potential benefit of certain exercise intensity with respect to infection rate, tumor recurrence, and survival is not known and requires further research. The American College of Sports Medicine recommends moderate to vigorous exercise intensities but also points out the

limited evidence behind the given recommendations for CRC patients and survivors [49].

The picture is less clear with regard to changes in psychological strain. One single study was able to investigate effects of inpatient rehabilitation treatment due to the controlled design and reported no effect on distress 12 months after treatment [43]. One possible explanation for the negative findings might be the short and non-cancer-site-specific rehabilitation program. In comparison to the other included studies, the multidisciplinary program consisted of a short 6-day workshop for breast, prostate, and colorectal cancer patients that mainly included peer-group sessions and lectures rather than individual tailored 3/4-week treatments involving frequent one-to-one therapy sessions with rehabilitation professionals [45]. The only randomized study was also limited by ineffective randomization with respect to initial distress and lack of follow-up of many non-receivers (intervention group), who tended to be less distressed at baseline. Reported changes from baseline to 1 and 6 months after the intervention were adjusted by cancer-site [45] and score changes from baseline to 12 months after the intervention was not provided [43]. Therefore, we could not draw a direct comparison to the findings of the included observational studies. Two other studies came to different conclusions regarding the endpoints anxiety and depression. One study reported a decrease of anxiety and depression level during rehabilitation [40] and the other study did not observe a decrease over time [39]. Based on the limited evidence, no conclusion can be made. However, a reduction of anxiety and depression [46] as well as psychosocial stress levels [48] during inpatient rehabilitation among cancer patients has been reported previously. With regard to positive changes on the physical level, CRC patients appeared to benefit most from rehabilitation therapy when compared to other cancer patients [33,35,39]. This aspect could be related to stronger physical impairments among CRC at admission in comparison to breast or prostate cancer patients [31,39]. In contrast, CRC patients may experience a greater psychological burden after rehabilitation. A study by Mehnert et al., for example, identified CRC, hematologic, and skin cancer as one predictor for persistent fear of recurrence after inpatient rehabilitation therapy in cancer patients. Higher levels of fear of recurrence in CRC patients might be partially related to general poorer prognosis than for example in breast or prostate cancer patients [34]. In addition to psychological strain, cancer patients are under risk experiencing financial strain, which seems to remain or even increase after rehabilitation as observed in two included studies [31,39]. The findings might reflect accumulating out-of-pocket payments for medical care and/or ongoing temporary or permanent disability in younger working patients.

The included observational studies, which followed-up participants 6 months or longer, indicate that the improved health status after rehabilitation may decrease over time. A recurrent increase in symptoms after the rehabilitation stay has also been described in other studies [33,34]. Cancer patients might struggle with applying recommendations and learned coping strategies in daily life. Furthermore, there is

no systematic and comprehensive after-care provision by local rehabilitation professionals in order to consolidate treatment success and respond to emerging health conditions.

Methodological quality of included studies and implication for future studies

The methodological quality of the included studies was fair. However, there are several limitations with regard to the answer to our research questions. First, except in three studies [35,40,43], the numbers of included CRC patients were low (<100). The small sample size likely hindered further stratification by potentially relevant factors such as cancer stage, time-since-diagnosis, completeness of treatment, and age for most analysis. In order to investigate changes in physical and psychological health as well as potential determinants of treatment success with adequate statistical power, higher numbers of CRC patients would be needed. Disclosure of such determinants would be essential for identifying individuals, who have rehabilitative needs but show no or no long-term improvement despite standard rehabilitative measures. Due to the different scope of some studies, authors provided cancer-specific descriptive values of the assessed health outcomes but no information about inferential statistics [31,35,39,40]. Among those that performed statistical testing, significance levels were often not reached likely due to limited statistical power. Second, the study populations of many studies were restricted to patients below 70 or 75 years [37–39,41,42]. Except for two studies [31,35], we observed a low mean age (57–62 years) or median age (54–63 years) of the included participants, whereas the median age at the time of diagnosis for CRC is about 70 in developed countries [50]. Thus, the evidence is limited to the large proportion of older CRC patients. Third, the length of observational periods varied from treatment period only [35,41,42] to 3–12 months after rehabilitation. Only studies with longer observation periods beyond the time of discharge were able to evaluate the potential benefit of inpatient rehabilitation in the everyday environment. Eventually, only one study included a comparison group (non-rehabilitants). Due to the lack of control groups, one cannot draw explicit conclusions about the effectiveness of treatment. An initial improvement in health status after the completion of active treatment seems likely with or without rehabilitative treatment. In order to establish evidence on the effectiveness of inpatient rehabilitation, RCTs would be highly desirable. However, in countries where inpatient rehabilitation is an established integral part of routine care, conducting studies with random treatment allocation would be difficult to conduct. Wait-list control groups and matched-pair-analysis, such as propensity score analysis, might be considered as possible alternative approaches to limit potential confounding as far as possible. Interventional studies with active controls or observational cohort studies could also enable some conclusion on the effectiveness of specific elements of rehabilitation therapy within patient cohorts.

Strengths and limitation of this review

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

Conclusions

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

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