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Abstract

Aim: Colorectal cancer survivors are one of the most rapidly growing groups of patients living with and beyond cancer. In a national multidisciplinary setting, we have examined the extent of late treatment-related sequelae in colorectal cancer survivors and present the scientific evidence for management of these conditions in this patient category with the aim of facilitating identification and treatment.

Method: A systematic search for existing guidelines and relevant studies was performed across 16 and 4 databases, respectively, from inception to 2021. This yielded 13 guidelines and 886 abstracts, of which 188 were included in the finalized guideline (231 included for full text review). Secondarily, bibliographies were cross-referenced and 53 additional articles were included.

Results: Symptoms have been divided into overall categories including psychosocial, bowel-related, urinary, sexual (male and female), pain/neuropathy and fatigue symptoms or complaints that are examined individually. Merging and grading of data resulted in 22 recommendations and 42 management strategies across categories. Recommendations are of a more general character, whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

Conclusion: Treatment-related sequelae in colorectal cancer survivors are common and attention needs to be focused on identifying patients with unmet treatment needs and the development of evidence-based treatment algorithms.

KEYWORDS
colo-rectal cancer, colon cancer, long-term sequalae, rectal cancer, sequelae, treatment-related sequelae

INTRODUCTION

In 2020, colorectal cancer (CRC) was the third most commonly diagnosed malignancy in the world, with almost 2 million new cases. CRC was also the second most common cause of cancer death worldwide, causing almost 1 million deaths [1]. Significant improvements in survival have been achieved owing to evolving treatment modalities and screening initiatives, which promote earlier diagnosis. Almost two-thirds of CRC survivors are alive 5 years after their diagnosis [2], and in Denmark the current 5-year survival is 71.3% [3]. Additionally, a substantial increase has been recorded in the incidence of CRC [2]. Thus, CRC survivors are one of the most rapidly growing groups of patients living with and beyond cancer.

Cancer survivorship has evolved to become more than a measure of time; focus has broadened to encompass the survivor, his or her quality of life (QoL) and survivorship care as well as epidemiological concerns related to survival rates, morbidity and mortality [4].

Whereas clinical practice guidelines exist for diagnosis and treatment, only a few evidence-based clinical guidelines on survivorship care have been published. The National Comprehensive Cancer Network (NCCN) has developed consensus-based guidelines on the treatment of patients with colon and rectal cancers that also include some recommendations regarding follow-up care after completion of treatment [5, 6]. In addition, the NCCN has developed survivorship care guidelines addressing long-term or late occurring psychosocial and physical problems and preventive health measures [7]. The American Society of Clinical Oncology's (ASCO's) clinical practice guidelines for cancer survivorship care focus on the prevention and management of symptoms experienced by survivors of a wide range of cancers. To date, ASCO has released three evidence-based cancer survivor care guidelines focused on fatigue, anxiety and depression, and neuropathy [8].

This guideline examines the extent of late treatment-related sequelae (TRS) in CRC survivors and presents the scientific evidence for management of late TRS in this patient category. Symptoms have been divided into overall categories including psychosocial, bowel-related, urinary, sexual (male and female), pain/neuropathy and fatigue symptoms or complaints that are examined individually.

METHOD

Target population and user

This guideline applies to all CRC survivors and was developed to support clinical decision-making and quality improvement. Thus, the target users are healthcare professionals working within CRC treatment and follow-up.

Search strategy

A systematic search of the electronic databases Pubmed Central, Cumulative Index of Nursing and Allied Health Literature (CINAHL) and Embase was conducted using the Medical Subject Headings (MeSH) rectal neoplasms or colonic neoplasms or colorectal neoplasms with relevant subheadings and by specifying the following limits: species (human), languages (English). The search included studies from the date of inception to February 2021. A search in the Cochrane Library was also conducted. The word concepts used for the search were: survivorship, late adverse effect, late toxicity, late effect and bowel dysfunction, urinary dysfunction, sexual dysfunction, psychosocial, quality of life, pain and neuropathy. All the synonyms and associated sub-terms were combined using the 'OR' operator, and subsequently these were combined along with the other concepts by the 'AND' operator. One reviewer (SH) independently screened the titles and the abstracts of each reference. A total of 231 articles were retained for full-text review and then screened by a minimum of two reviewers to assess their quality and determine with evidence level: 188 were included in the finalized guideline. Further searches for relevant reference literature from related fields provided an additional 53 articles that were also included in the guideline.

Guideline template, concept and approval

The guideline template is based on the six domains listed in AGREE II (Appraisal of Guidelines Research and Evaluation Tool) [9]. The Danish Multidisciplinary Cancer Group's guidelines concept, template and guidance papers seek to incorporate principles from leading organizations within the guidelines area, such as the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [10], the National Institute for Health and Care Excellence (NICE) [11] and the Oxford Centre for Evidence-Based Medicine [12]. The guideline content was approved by the disease-specific Multidisciplinary Cancer Group, whereas the format was approved by the Centre for Clinical Practice Guidelines on Cancer in Denmark.

Evidence assessment and articulation of recommendations

A minimum of two panel members were assigned to each of the symptom categories. These members individually extracted data and graded the quality of evidence and the strength of the recommendation into a shared internet-based platform using the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations [12]. These data were then merged and discussed in plenum (in case of discrepancies) before the final wording of recommendations and management strategies was prepared. Recommendations are of a more general character, whereas

management strategies provide more practical advice suited for initiation on site before referral to specialized units.

Relevant data in each symptom category were extracted from each article by the assigned members of the panel and shared on an internet-based platform. A draft of each symptom category was produced by SH, apart from bowel dysfunction in colon cancer patients (drafted by JF) and pain/neuropathy (drafted by CJSK and LV). Panel members assigned to the relevant symptom categories reviewed the drafts and the approved versions were then compiled into the guideline, which was finalized by the entire group of panel members.

Stakeholder involvement

The group behind these guidelines comprised two oncologists (CJSK and LV), several surgical gastroenterologists (KJE, PC, BTO, PMF, RAH, NAF and SH), a medical gastroenterologist (JF), a stoma nurse specialist (MK), a sexologist (AHM) and a urologist (CHG). No patients were involved in the development of these guidelines.

SCIENTIFIC EVIDENCE

Literature review and evidence description of TRS in follow-up in CRC survivors (Figure 1)

Survivors of CRC develop a combination of health, information and support needs due to their diagnosis. New challenges specific to the nature of the treatment require significant practical and psychological support to facilitate adjustment [13] (2b). The overall health and QoL experienced by survivors are influenced partly by the stage at diagnosis and the types and duration of therapy given [2] (2a) and partly by the type of cancer affecting the patient [rectal cancer (RC) survivors report a greater need for interventions than colon cancer (CC) survivors] and age at diagnosis [14–17] (2b).

A substantial risk exists that surveillance for cancer recurrence may be prioritized over the management of any TRS, and provision of information for and support to survivors. Haggstrom et al. [18] reported that just 7% of CRC survivors saw a medical professional for management of TRS whereas 85% attended follow-up tests [18] (3a).

The lack of focus on TRS is well documented in a recent review of current European guidelines on post-CRC follow-up. The review showed significant variation in terms of follow-up intervals and methods and revealed that identification and treatment of TRS received only limited attention. More specifically, the authors found that management of TRS was mentioned in only 12 of the 21 guidelines and was recommended explicitly in only four [19] (2a). Wiltink et al. found 51 CRC (including anal cancer) guidelines, among which only 13 (25%) included recommendations on how to manage TRS [20] (3a).

Patients reported positive perceptions of CRC surveillance in 75% of the studies included in a recent review. Positive perceptions included high rates of overall satisfaction with follow-up care, with one study identifying a correlation between a longer patient–physician relationship and the perceived quality of follow-up care [21] (3a). In 37.5% of the included studies, negative perceptions of follow-up were also described. These included anxiety or stress related to follow-up visits or tests, unmet expectations regarding information exchange, lack of psychosocial evaluation and emotional support, and overall dissatisfaction [21] (3a). Patients were dissatisfied with the available information regarding how the treatment would affect their body and sexuality. Furthermore, patients expressed dissatisfaction with communication between providers and the extent to which their family was included and considered in care planning. The review identified room for improvement in information exchange, sensitivity towards psychosocial and QoL issues and emphasis on general health maintenance and prevention. This was supported by a 2019 cross-sectional study reporting that more than two-thirds of Irish CRC survivors reported unmet information needs (68%) or social difficulties (66%), whereas 40% reported some dissatisfaction with continuity of care. Greater social difficulty was

Focus on treatment-related sequelae in follow-up

Recommendations

- **Follow-up programs beyond standard is not recommended. Increased frequency of follow-up visits has little or no effect on quality of life (QoL), anxiety, and depression (Grade A).**

- **Systematic monitoring of quality of life-related and treatment-related sequelae following treatment to identify patients who require further specialist evaluation or support after treatment, and to offer optimal tailored treatments is recommended (Evidence level 5) (Grade D). Monitoring should employ selected validated patient-related outcome measures (Grade B).**

FIGURE 1 Guideline recommendations concerning follow-up programmes for colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations.

consistently associated with a poorer QoL in all domains, whereas lower satisfaction with continuity of care predicted a poorer physical, social, functional and overall QoL [22] (3a).

Intensified follow-up programmes have been suggested to improve overall patient outcomes: a meta-analysis comprising six reviews found that intensified follow-up programmes were associated with a survival benefit (OR 0.73; 95% CI 0.59–0.91) but reported no impact on QoL [23] (2a). Conversely, a more recent systematic Cochrane review including 19 studies found that intensified follow-up programmes had little or no effect on the overall survival of CRC patients, little or no effect on CRC-specific or relapse-free survival and little or no effect on QoL, anxiety or depression [24] (1b). Similarly, a large international randomized controlled trial (RCT) of standard versus intensified follow-up including 2509 patients found no significant survival benefit of intensified follow-up [25] (1b).

As the outcome of primary treatment of CRC is improving, the potential benefits of cancer surveillance for recurrence of cancer seem to be declining [26] (5). Consequently, we are facing a growing need to change our standard follow-up programmes and to personalize them, thereby covering many additional aspects [26] (5). Various randomized approaches have attempted to tailor follow-up care to the need of CRC patients. However, many of these approaches have failed to significantly improve patients' health-related QoL (HR-QoL) [25, 27, 28] (1b). Even so, patients were more satisfied with tailored follow-up care programmes than with usual care. Possibly, survivorship care may be an effective intervention in a more targeted population, perhaps including patients with higher levels of distress or patients with greater levels of unmet need [27] (1b). Models specifically targeting CRC survivors with unmet needs seem beneficial – either by open access to the clinic rather than standard clinical visits or by risk stratification [25, 29] (5). However, further evidence is needed regarding the optimal approach for tailored follow-up.

Patient-reported outcome measures (PROMs)

The most widely used PROM to measure QoL after cancer treatment is The European Organization for Research and Treatment of Cancer core questionnaire (EORTC QLQ C-30), together with the site-specific CRC module (EORTC QLQ CR-38/29) [30]. The EORTC QLQ-38/29 consists of 38 [30] items covering symptoms and sequelae related to various treatment modalities, body image, sexuality and future perspective. The Danish version of EORTC QLQ CR-38 has been validated and showed satisfactory psychometric properties for the scales of body image, sexual functioning, male sexual problems and defaecation problems. Suboptimal psychometric performances were found for the scales of micturition problems, symptoms of the gastrointestinal tract and weight loss. It was not possible to assess the psychometric properties of female sexual problems and sexual enjoyment scales due to a large number of missing values [31]. EORTC QLQ-38/29 has been validated in more than 70 countries and has currently been translated into 108 languages. However, the measurement properties of EORTC QLQ-38/29 were evaluated in a recent systematic review which concluded that these properties were limited [32] (2a). The review called for better quality research on the measurement properties of QLQ-CR29 and concluded that future validation studies should focus on assessing the structural validity and subsequently its internal consistency on unidimensional subscales. Further issues that should be examined included reliability, and thereby measurement error, construct validity and responsiveness with a priori hypotheses, and cross-cultural validity.

More specific PROMs for in-depth understanding of specific symptoms, screening and monitoring are listed in Table 1. Numerous instruments have been developed in different contexts and populations, ranging from screening tools and cancer site-specific tools to more comprehensive tools for research purposes, but there is great variation in the quality and validity of these. We have focused on tools that are most commonly used, have been specifically developed for CRC survivors or have previously been used in a CRC context, preferably with a Danish version.

Using an internet-based survival care plan platform, a study found that for lower gastrointestinal (GI) cancer survivors (including 792 CC survivors and 218 RC survivors), it was feasible to obtain PROMs from an Internet-based survivorship tool. Survivors reported a wide range of late and long-term sequelae, and these were used for counselling at the time of diagnosis and to help anticipate and respond to disease- and treatment-related sequelae during follow-up [33] (4).

A PROM-based, prospective cohort study including 1721 CRC survivors invited patients to complete a survey about TRS at 3, 12, 24 and 36 months after surgery as part of their follow-up, with an 80.5% participation rate. Patients were asked if they wished to be contacted by telephone in relation to TRS. Contact was requested by 19.0% of CC survivors and a total of 8.4% were referred for TRS treatment, primarily due to bowel dysfunction. In the RC group, contact was requested by 30.8%, and 16.2% were referred for TRS treatment, mainly due to bowel and sexual dysfunction. If requested, contact was made regardless of the PROM score [14] (2b).

Psychosocial distress in CRC survivors (Figure 2)

Cancer is a traumatic event. Cancer survivors often face adaptation problems, fear of cancer recurrence (FCR) and negative effects of cancer treatment. Furthermore, a significant proportion of CRC survivors experience anxiety, depressive symptoms or reduced mental well-being [34, 35] (2b).

A 2010 systematic review found that, despite a good overall QoL, CRC survivors had poorer depression scores than the norm and suffered from long-term symptoms such as distress regarding cancer. The same review found that higher levels of depression and anxiety were significantly associated with lower values of global QoL, physical functioning, role functioning, cognitive functioning, emotional functioning and social functioning scales over time [36] (3a). Time since diagnosis is associated with fewer depressive symptoms, but not with fewer anxiety symptoms [37] (2b). Screening for

TABLE 1 PROM tools for specific symptom categories

Author	Symptom category	Tool	Outcome
Jacobsen, Donovan et al. 2005 [216]	Psychosocial	Distress Thermometer (DIS-A)	A rating scale from 0 (no distress) to 10 (extreme distress), in which a score of 4 or higher suggests a level of distress of clinical significance. In addition, a 38-item 'Problem list' asks patients to identify their problems within five categories: practical, family, emotional, spiritual/religious and physical. The tool is recommended by the NCCN and has been translated into numerous languages. The tool is easy to administer and empowers the clinician to facilitate appropriate psychosocial support and referrals
Campbell, H. Sanson-Fisher, et al. 2011 [217]	Psychosocial	(Short form) Survivor's Unmet Needs Survey [(SF)SUNS]	89-item (25) tool divided into five subcategories: emotional health needs (33 items), access and continuity of care (22 items), relationships (15 items), financial concerns (11 items) and information needs (8 items).
Zigmond, Snaith (1983) [218]	Psychosocial	Hospital Anxiety and Depression Scales (HADS)	14-item tool: depressive symptoms (7) and anxiety (7) evaluated in the past week. Answered on a four-point Likert scale; the total score for each scale ranges from 0 to 21
Simard, Savard (2009) [219]	Psychosocial	Fear of Cancer Recurrence Inventory (FCR-I)	42-item tool evaluating seven fear of cancer recurrence components (triggers, severity, psychological distress, functioning impairment, insight, reassurance and coping strategies)
Emmertsen, Laurberg (2012) [73]	Bowel dysfunction (low anterior resection syndrome)	Low Anterior Resection Syndrome Score (LARS score)	Five subcategories: incontinence for flatus, incontinence for liquid stool, faecal frequency, clustering of (less than an hour between) bowel movements, and urgency. The response score values are based on the impact of the particular symptom/frequency combination on QoL. The total score ranges from 0 to 42 points with 0–20 points meaning no LARS, 21–29 minor LARS and 30–42 major LARS
Temple, Bacik, Savatta, et al. (2005) [220]	Bowel dysfunction (low anterior resection syndrome)	Memorial Sloan Kettering Cancer Center Bowel Function Instrument (MSK-BFI)	18 questions within a 4-week recalling timeframe. Grouped into three subscales (diet, urgency/soilage and frequency). The MSK-BFI total score ranges from 18 to 90 with a score of 90 indicating the best possible bowel function measured with this questionnaire
Grant, Ferrell, Dean, et al. (2004) [221]	Stoma function/impact	Modified City of Hope Colorectal Cancer Quality of Life Questionnaire Ostomy (MCOHQOLQO)	43 items categorized into four subscales: physical health, psychological, social and spiritual well-being. All items are Likert-scale questions with grades from 0 to 10. Total subscale scores are calculated by adding scores of all scale items and then dividing the total score by the number of items in each subscale
Prieto, Thorsen, Juul (2005) [222]	Stoma function/impact	The Stoma QOL Questionnaire	20 items with four response options ('Always' (1), 'Sometimes' (2), 'Rarely' (3), 'Not at all' (4)). Focuses on four areas in which a stoma may impact QoL: sleep, sexual activity, relations to family and close friends and social relations other than family and friends. Score ranging from 20 to 80, with higher scores indicating a better QoL
Thyø, Emmertsen, Pinkney, et al. (2017) [223]	Stoma function/impact	The Colostomy Impact Score (CIS)	Seven-item tool (odour, leakage, stool consistency, pain at the stoma site, skin problems, herniation and stoma management help) with a total range from 0 to 38 points. A score of ≥10 indicates a major impact of colostomy

TABLE 1 (Continued)

Author	Symptom category	Tool	Outcome
Barry, Fowler, O'Leary, et al. (1992) [224]	Urinary dysfunction	The International Prostate Symptom Score (IPSS)	Developed for assessment of benign prostatic hyperplasia. This tool includes seven items: incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining and nocturia
Abrams, Avery, Gardener, Donovan, ICIQ Advisory Board (2006) [225]	Urinary dysfunction	The International Consultation on Incontinence Modular Questionnaire – Male/ Female Lower Urinary Tract Symptoms (ICIQ-MLUTS and ICIQ-FLUTS)	Evaluates symptoms regarding both regular urinary tract symptoms and the most prominent symptoms following pelvic surgery. By adding up the prevalence scores of the individual items, a voiding symptoms subscale (0–20) and an incontinence symptoms subscale (0–24) can be calculated. There is no defined cut-off point for good versus poor function
Rosen, Riley, Wagner, et al. (1997) [226]	Sexual dysfunction (male)	International Index of Erectile Function (IIEF)	Multidimensional, self-administered questionnaire comprising five domains: erectile function, orgasmic function, intercourse satisfaction, sexual desire and overall satisfaction
Rosen, Brown, Heiman, et al. (2000) [227]	Sexual dysfunction (female)	Female Sexual Function Index (IFSF)	19-item questionnaire assessing key dimensions of female sexual function. It was developed for healthy patients and does not consider cancer-related symptoms
Jensen, Klee, Thranov, Groenvold (2004) [228]	Sexual dysfunction (female)	Sexual Function Vaginal Changes questionnaire (SVQ)	17-item instrument that addresses the key dimensions of female sexual dysfunction and vaginal problems in patients with gynaecological cancer
Thyø, Emmertsen, Laurberg (2018) [160]	Sexual dysfunction (female)	The Rectal Cancer Female Sexuality Score	Seven-item tool with weighted scoring values based directly on QoL impact. The values are added to yield a total score ranging from 0 to 29 points. A score ≥9 indicates sexual dysfunction
Mortensen, Thyø, Emmertsen, Laurberg (2019) [229]	Chronic pain (impact on QoL)	Rectal cancer chronic pain score	Six items tool evaluating pain frequency, common intensity, intensity when most severe, duration, disruption of night's sleep and giving up daily activities. Options are assigned numerical values from 0 to 12, with a total range of 0–45 and three classification groups: 0–7 for no significant pain, 8–17 for minor pain syndrome and ≥18 for major pain syndrome
	Chemotherapy-induced peripheral neuropathy	Common Terminology Criteria for Adverse Events (CTCAE)	This generally applied tool uses grades from 1 to 5 (1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, death)
Postma, Aaronson, Heimans, et al. (2005) [230]	Chemotherapy-induced peripheral neuropathy	The QLQ-CIPN20	20-item questionnaire specifically focusing on CIPN intended to supplement the core QoL questionnaire of the European Organization for Research and Treatment of Cancer
Yellen, Cella, Webster et al. (1997) [231]	Cancer-related fatigue	Functional Assessment of Cancer Therapy-Fatigue (FACT-F)	40-item tool, subdivided into four primary dimensions of QoL domains; physical well-being (7 items), social and family well-being (7 items), emotional well-being (6 items) and functional well-being (7 items), and 13 fatigue-related questions
Schwartz (1998) [232]	Cancer-related fatigue	The Schwartz Cancer Fatigue Scale	28-item tool with four subscales (physical, emotional, cognitive, temporal)

Note: This table is not exhaustive but focuses on tool specifically developed to assess preferably colorectal cancer or, if not, then cancer patients in general.

Abbreviations: CIPN, chemotherapy-induced peripheral neuropathy; LARS, low anterior resection syndrome; QoL, quality of life.

(Continues)

Psychosocial distress

Recommendations

- Survivors should be assessed for signs of depression and anxiety as a significant group of patients experience clinically relevant anxiety, depressive symptoms, or reduced mental wellbeing affecting quality of life (QoL) (Grade B).
- Assessment should be done at early follow up as depression may occur within three months of a colorectal cancer diagnosis (with attention to pre-existing depressive conditions) (Grade B).
- Fear of recurrence should be acknowledged and addressed as a large proportion of survivors report high levels of fear of recurrence characterized by higher levels of distress, post-traumatic stress symptoms, and a lower QoL (Grade B).
- Body image distress should be acknowledged and addressed. Particular attention should be paid to survivors of rectal cancer, ostomates, survivors with persisting bowel dysfunction, female and younger (age < 50 years) survivors (Grade B).
- Referral of patients with signs of clinical depression upon assessment for proper diagnosis and management is recommended (Grade D).

Management strategies

- Assessment of psychological distress should be performed using the Danish version of the Distress Thermometer (DIS-A) as a first step in identifying persons in need of support (Grade B).
- Physical activity and dietary interventions may affect QoL, but consensus is lacking in terms of both form and contents (Grade B)

FIGURE 2 Guideline recommendations concerning psychosocial dysfunction in colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

these symptoms is important, especially among survivors who are single, have a low level of education and comorbid conditions, even years after their CRC diagnosis and treatment.

Apart from recurrence of the disease, general and health-related factors such as age, social network size, income, education, body mass index (BMI) and a number of comorbidities may impact on QoL in CRC survivors [38, 39] (3a). Greater medical comorbidities, poorer self-reported general health, bowel dysfunction and physical symptom distress have all been correlated with poorer psychological outcomes [36] (2b). Further, the risk of having a poorer mental health-related quality of life (HR-QoL) among women has been found to be twice as high as this risk among men, whereas protective factors are age >70 years, retirement, being in a relationship and having a higher level of education [40, 41] (2b). Poorer mental HR-QoL scores may be indicative of psychosocial issues among CRC survivors that are not being adequately addressed, which would underscore the need to screen survivors for psychosocial distress and link them to appropriate support services [41] (2b).

Cancer stigma and self-blame affect a significant proportion of men with CRC and are independent predictors of depressive symptoms. A cross-sectional study among North American veterans with CRC found that 31% of respondents endorsed at least one item in a measure of cancer stigma, 10% indicated that it was at least 'a little true' that other people blamed them for their illness and 25% reported feeling that it was at least 'a little true' that they were to blame for their illness. All three independent variables were associated with depressive symptoms in bivariate models; cancer stigma and self-blame were significantly associated with depressive symptoms in the multivariate model [42] (2b).

However, long-term CRC survivors (>5–15 years after the diagnosis) seem to have an excellent overall QoL when compared with non-cancer controls [43] (2b). One explanation for the good overall QoL is the concept of reframing/response shift. This concept hypothesizes that CRC survivors either establish a new meaning of the concept of QoL or change the constitution of QoL dimensions. Another reason for the positive QoL assessment may be the finding of benefit in the cancer experience known as benefit finding or posttraumatic growth, both of which have been described for CRC survivors.

Specific aspects causing psychosocial distress in CRC survivors

Pre-existing depression or anxiety

Comorbidities that are classified as limiting by patients have been found to be significantly associated with a poorer global health status/QoL as well as poorer symptom and functioning outcomes, including increased fatigue, pain, urinary and bowel symptoms, and reduced physical, role, emotional, cognitive and social functioning [35] (2b). Depression/anxiety appears to have the greatest association with poorer outcomes, with clinically meaningful differences being recorded across all outcomes (except for urinary and bowel symptoms)

[35] (2b). In a prospective cohort study following 872 CRC survivors, approximately half of the patients stated that their depression/anxiety was not pre-existing but had been diagnosed after CRC. The authors found a stable prevalence of depression/anxiety 3 months after surgery and at the 5-year follow-up suggesting that diagnoses may often occur within 3 months of a CRC diagnosis [39] (2b).

Fear of cancer recurrence

Fear of cancer recurrence may be defined as the fear or worry that the disease will return or progress in the same organ or in another part of the body. Whereas a normal level of FCR may keep a person alert and aware of any symptoms, high levels of FCR may adversely affect a person's QoL and social activities [44] (2b). A cross-sectional study found that 38% of CRC survivors experienced high levels of FCR, characterized by higher levels of distress, posttraumatic stress symptoms and lower QoL. These individuals particularly reacted to disease-related triggers, felt helpless, were worried and experienced limitations in daily functioning [44] (2b). A systematic review found that even ≥5 years after their CRC diagnosis, many survivors were afraid of a recurrence, further spread of cancer or a second cancer, and showed distress regarding future diagnostic tests [36] (2b).

Body image distress

An English national PROM-based survey including 21,802 CRC survivors found that 10.1% of respondents reported body image distress and that this percentage was higher among RC survivors than among CC survivors (13.9% vs. 8.2%). Among ostomates (of whom the majority were treated for rectal cancer), 20.9% reported body image distress [45] (2b). Strong correlations have been found between a poorer body image, more severe depressive symptoms and a poorer QoL [46] (2b). A 2020 systematic review and meta-analysis of the symptom experience in CRC survivors found that among 10 postcancer treatment symptoms analysed, the pooled mean frequency was highest for body image distress, and it was rated the third most severe symptom by survivors [47] (2a). A cross-sectional study found that diarrhoea and GI symptoms are distressing and directly related to a poorer body image and greater depressive symptoms, but not to anxiety in female rectal and anal cancer survivors. Predisposing factors were young age and presence of a stoma [48] (3b). Among these women, 47% reported feeling less feminine due to their disease and treatment and 40% reported feeling less attractive. The development of body image distress may lead to an increased risk of depression. Periodic assessment of body image concerns in survivorship care may help identify the development of body image distress. One longitudinal study did find body image distress to decrease significantly over a period of 6 months [46] (2b).

Cognitive distress

The American Cancer Society's Colorectal Cancer Survivorship Care Guidelines recommend screening for cognitive decline in patients treated with chemotherapy as such therapy is associated with declining cognitive function, particularly for individuals who are younger than 70 years [2] (3b). In patients with lower GI cancer, cognitive changes were reported by 48.6% of patients at a mean 2.4 years after treatment [33] (2b). The symptoms reported by patients who complain of cognitive decline vary, but may include decreased executive functioning skills, longer processing time or reaction response time, diminished organizational skills, loss of language or math skills and/or difficulty with concentration or attention. These often translate into lower HR-QoL scores, especially as patients transition back to work [2] (2b). The NCCN Guidelines for Survivorship suggest screening for treatable causes that may aggravate cognitive impairment, such as depression and anxiety, although data are lacking for evidence-based recommendations regarding routine screening for cognitive decline in this population [2] (2b).

Monitoring and evaluation

A simple option is the Distress Thermometer (DIS-A), which is similar to the rating scale used to measure pain on a scale from 0 (no distress) to 10 (extreme distress), in which a score of 4 or higher suggests a level of distress of clinical significance. In addition, a 38-item 'problem list' asks patients to identify their problems within five categories: practical, family, emotional, spiritual/religious, physical. These tools are available from the NCCN Guidelines for Distress Management. Similarly, the Survivor Unmet Needs Survey (SUNS) and the Short-Form SUNS (SFSUNS) may be used to distinguish between problems that survivors experience and problems that they need help to manage across a range of life areas, including financial concerns, information and access, and continuity of care [2] (3b).

The Hospital Anxiety and Depression Scale (HADS) is designed to assess self-reported symptoms of anxiety and depression [38] (3b). The HADS consists of 14 items: seven items for depressive symptoms and seven items for anxiety. It assesses levels of symptoms in the past week. The questions may be answered on a four-point Likert scale, and the total score for each scale ranges from 0 to 21 [42] (3b).

The Fear of Cancer Recurrence Inventory (FCRI) is a multidimensional measure for FCR. The translated Danish version of the FCRI has been found to be a valid measure of FCR in a population of CC patients and was shown to identify patients with a need for special attention or interventions for high levels of FCR [43] (3b).

Failure to address psychosocial concerns may have significant health consequences in the form of depression and anxiety, lower QoL, lack of adherence to recommended surveillance protocols and even lower survival rates [22] (3a).

Treatment options

Diet and exercise

A systematic review of the impact of nutritional interventions on QoL concluded that they seem to augment the health and QoL of CRC survivors [49] (2a). A more recent RCT assessed the effects of dietary and physical activity (PA) interventions on generic and cancer-specific QoL, anxiety and depression levels among adult

Chinese CRC survivors measured at baseline and at 6, 12, 18 and 24 months during/after a 12 month intervention. The authors found that participants receiving dietary intervention experienced a significant improvement in the generic measure of QoL at 12 months in the cancer-specific QoL scores, and in levels of depression at both 12 and 24 months of follow-up, but no significant changes were found in the levels of anxiety. Furthermore, participants receiving PA intervention only demonstrated a significant improvement in physical functioning at 6 months [50] (1b).

The effect of PA on HR-QoL has previously been established in a systematic review, which concluded that besides the obvious benefits of regular PA on general health and cancer recurrence, improved PA provided a positive contribution to HR-QoL. However, a lack of consensus and conclusive evidence exists regarding how such a programme should be designed in terms of both its form and content [50-52] (1b). A 2020 systematic review and meta-analysis of exercise interventions in CRC survivors found no evidence of the effect of exercise on psychosocial outcomes (QoL, fatigue, anxiety and depression) [53] (2a).

Psychosocial interventions

A 2016 systematic review evaluating 14 RCTs with a minimum of one psychosocial or QoL outcome (including 2476 CRC survivors) examined the effect of psychosocial interventions on QoL and psychosocial outcomes for CRC survivors of all disease stages. Psychosocial interventions were defined as group and/or individual psychotherapy or cognitive-behavioural training aiming to modify maladaptive thoughts and behaviours [34] (1b). Of the 14 RCTs, only three showed significant effects of the intervention on multiple mental health outcomes. These interventions included written and verbal emotional expression, progressive muscle relaxation training and a self-efficacy-enhancing intervention. Three additional intervention trials showed an impact on outcomes related to mental health and QoL, including studies testing an Eastern body–mind–spirit intervention, nurse-administered information packets on RC and its treatment, and an intimacy enhancement intervention for patient–partner dyads [34] (1b). Most studies (10/14) used an individual delivery approach, and the number of sessions ranged from 1 to 12, with the exception that three studies did not have a standard number of sessions. Most studies (10/14) compared the intervention with standard care, and only one study included a comparison arm that controlled for time and attention given to participants. The review concluded that, overall, empirical support was limited for psychosocial interventions for CRC patients, and that further work is needed to address the unique QoL concerns of this population, such as embarrassing side effects of treatment and sexual dysfunction [34] (1b).

Bowel dysfunction in CRC survivors

Bowel dysfunction after colon and rectal cancer is discussed separately, as both needs and pathology differ substantially.

Bowel dysfunction after colon cancer (CC) (Figure 3)

Late GI TRS are common following surgery for CC. They include a broad spectrum of symptoms: loose to liquid stool (14.2%–45.3%), faecal incontinence (6.2%–34.1%), faecal urgency (9.3%–37.2%), nocturnal defaecation (20.2%–32.1%), incomplete evacuation (26.4–66%) and obstructive, difficult emptying (14.9%–71.1%) needing aid when defaecating (14.2%) [54–57] (2b). The GI symptoms have a negative impact on QoL and show no improvement over time [54–56] (2b).

Bowel dysfunction after right-sided hemicolectomy

In a recent cross-sectional study including 3306 right-sided hemicolectomy patients, the authors found that patients reported loose stools (15.5%), were incontinent for loose stool (28.8%), experienced urgency daily (18.8%) and suffered from nocturnal defaecation (20.2%) significantly more than controls. They found no difference when comparing symptoms of obstruction, incomplete evacuation, use of laxatives or bloating. Furthermore, the authors concluded that adjuvant chemotherapy (given in 34% of cases) did not affect bowel function or QoL [55] (2b).

In support, a review found that one in five right-sided hemicolectomy patients had loose stool, increased bowel frequency and/or nocturnal defaecation [57] (3a).

The literature on monitoring and need for investigation and treatment of bowel dysfunction after a right-sided hemicolectomy is scarce. In a multicentre cohort study, 953 patients with previous CC were invited to complete a PROM. The study recorded a response rate of 80.5%. Among these, 9.9% responded with a request for further investigation and treatment even though more patients reported bowel dysfunction in their PROM. The referred patients' primary symptoms were urgency (65%) and fragmented stools (70%). Among the patients referred for treatment, 56.8% were women with a right-sided hemicolectomy. Among these, 54% had loose stools and 62% were faecally incontinent [58] (2b).

Aetiology of symptoms. Only a few studies have investigated the aetiology of chronic diarrhoea following a right-sided colectomy for CC. A recent study investigating 45 symptomatic and 19 asymptomatic right-sided hemicolectomy patients found that 82% of cases had bile acid malabsorption [BAM; defined as a selelium-75 homocholic acid taurine (SeHCAT) scan <15%] versus 39% of controls, whereas approximately 70% of both cases and controls had small intestinal bacterial overgrowth (SIBO; positive breath test for hydrogen or methane) (Larsen et al. unpublished) (2b). The authors found no association between BAM and SIBO, or between diarrhoea and SIBO. However, treatment with antibiotics produced sufficient symptom relief in 16% of patients with both SIBO and BAM. In the patients treated for BAM with a bile acid binder and/or a fat-reduced diet, defaecation frequency, Bristol stool type, urgency and faecal incontinence were all significantly improved.

In a previous study, all of 14 patients with chronic diarrhoea and previous caecal cancer were diagnosed with BAM (SeHCAT < 15%)

Bowel dysfunction after colon cancer

Recommendations

- Colon cancer survivors should be offered routine screening for bowel dysfunction (Grade B).
- In case of chronic diarrhea, it is recommended to refer colon cancer survivors to a gastroenterologist for further investigations (Grade D).
- It is recommended to offer referral of patients with persisting symptoms for treatment in specialized units (Grade D).

Management strategies

- Ruling out underlying 'organic' lesions that may explain a patient's symptoms after surgery is a prerequisite for treatment (Grade D).
- Bile acid malabsorption should be treated with a low-dose bile acid binder (colestyramine 4 g) at nighttime to avoid side-effects and interaction with other medicines (Grade D). Additional benefit may be gained by adding a fat-reduced diet. Fat-reduced diet may also be a first-choice treatment according to the se-hcat scan result (Grade C).
- Symptomatic small intestinal bacterial overgrowth is treated with rifaximine as this antibiotic has the best-established dose-related effect (Grade A). A dose of 600 mg x 2 for six days is recommended (Grade D).
- Treatment with anti-diarrheal or laxatives should follow recommendations for treatment of idiopathic diarrhea and constipation (Grade D).
- Patients with chronic constipation/obstructive defecation syndrome or low anterior resection syndrome (LARS)-like symptoms with no effect of laxatives could be offered transanal irrigation (Grade D).

FIGURE 3 Guideline recommendations concerning bowel dysfunction in colon cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

[59] [5]. In addition, a recent review concluded that a positive association exists between the resected length of terminal ileum, loss of bile acid and diarrhoea [60] (3a).

Bowel dysfunction after left-sided hemicolectomy/sigmoid resection

A large cross-sectional study including 3061 patients with a previous sigmoid resection due to cancer reported that 17.9% of patients presented with obstructed defaecation symptoms (ODS) compared with 7.3% of polypectomy controls [56] (2b). The most prevalent symptoms were nocturnal defaecation (32.1%), use of aid during defaecation (24.2%), fragmentation of stools at least weekly (21.5%), daily bloating (20.4%) and a sense of outlet obstruction at least weekly (14.9%). The adjusted OR for ODS after a sigmoid resection was 2.57. Predictive factors were female gender and smoking. ODS was associated with a substantially impaired QoL. Applying the low anterior resection syndrome (LARS) score, significantly more patients than controls had major LARS. Predictive factors for LARS in the colon group were female gender and a previous stoma. Major LARS was associated with impaired QoL [56] (2b). In a retrospective cross-sectional study from the Netherlands, 51.2% of patients with a rectal resection reported major LARS compared with 20.4% of patients with a sigmoid resection and 14.3% of patients with a left-sided hemicolectomy [61] (2b).

Monitoring and evaluation

Attention to late GI TRS after CC is relatively new. Therefore, no PROMs for screening, monitoring or grading of bowel dysfunction

after a right- or left-sided hemicolectomy exist. Previous studies have used the EORTC QLQ-38 [30], the Wexner Fecal Incontinence Score, the LARS score or the McDonald & Heald Continence Grades to evaluate and compare the significance of bowel dysfunction between types of colectomy [54] (2b). Although a review and meta-analysis found no significant difference between scores after a right- or left-sided hemicolectomy [54] (2b), it seems that the overall symptom pictures and aetiology of symptoms differ according to the resection performed [55, 56, 61] (2b).

Treatment options

Physicians should ensure that no underlying 'organic' lesion may explain a patient's symptoms after surgery (e.g. mucosal lesion, anastomotic stricture, local recurrence) [6].

Bile acid malabsorption is generally treated with a bile acid binder. However, Gupta et al. have proposed a multidisciplinary approach with bile acid sequestrants and/or a fat-reduced diet advised by a dietician depending on the SeHCAT scan results when treating BAM in cancer survivors (SeHCAT 15%–20%, solely a fat-reduced diet; SeHCAT 10%–14.9%, a fat-reduced diet with or without a bile acid binder; SeHCAT 5%–10%, a bile acid binder with or without a fat-reduced diet; SeHCAT <5%, a fat-reduced diet and treatment with a bile acid binder). In the study, 70% of patients reported significant symptom relief [62] (4). In support, Jackson et al. applied the algorithm in patients previously treated for cancer and diagnosed with BAM and showed a significant reduction in abdominal pain

and nocturnal defaecation [63] (4). Side effects to bile acid binders are often dosage dependent and the bile acid binder is prone to interact with other medications. Thus, a low initial dosage at night-time is preferable, with gradual titration for optimal effect [58] (5). Colestyramine should be the first choice. If no effect is achieved, coleveselam may be attempted as up to 70% of patients will respond positively despite no effect of colestyramine [58] (5).

Small intestinal bacterial overgrowth is generally treated with antibiotics. Rifaximine is the antibiotic with the best established and dose-related effect [65] (1b). Based on that trial, we recommend using rifaximine, 600 mg×2 for 6 days [6]. Due to the price of rifaximine, ciprofloxacin 500 mg×2 for 7 days, metronidazole 500 mg×3 for 7 days or amoxicillin/clavulanic acid 500/125 mg×3 for 7 days are often used despite a lack of evidence.

Antidiarrhoeal medications comprise fibre supplements, loperamide and opioid tincture. Evidence is based on studies on chronic idiopathic diarrhoea and diarrhoea-predominant irritable bowel syndrome (IBS) and is not specific to cancer survivors [55] (5).

Laxatives for chronic constipation comprise osmotic and peristaltic laxatives and second-line treatment with prucalopride (Resolor®) or linaclotide (Constella®). Evidence is based on studies on chronic idiopathic constipation and is not specific to cancer survivors [67] (5).

Nonpharmacological treatments may include transanal irrigation (TAI) for chronic constipation/ODS with major symptoms of LARS [68, 69] (5) and, in the case of intractable bowel dysfunction, evaluation of indications for a colostomy.

Dietetic intervention. One third of CC patients report that their diet affects their bowel function negatively (Borre et al. unpublished) (2b). The food items most commonly reported to have a negative impact on bowel function are fat, spices, sweets and meat, whereas vegetables, fruit and dairy products are the items most frequently reported to have a positive impact on bowel function. Interestingly, more than 90% of clinicians state that they give dietary advice to CC patients whereas only 24% of patients believe that they have received such advice. An unmet need exists for intervention studies focusing on dietary treatment principles to establish the role of dietetic interventions in CC patients.

Bowel dysfunction after rectal cancer (Figure 4)

Due to surgical advances made in recent decades, an increasing number of RC patients will undergo sphincter-preserving surgery (SPS) with a low colorectal or coloanal anastomosis to avoid permanent colostomy. Unfortunately, 30%–80% of RC patients develop a change in bowel habit including faecal incontinence, urgency and frequent bowel movements [70, 71] (2a). In a systematic review, the most frequently reported symptoms were incontinence (97%), stool frequency (80%), urgency (67%), evacuatory dysfunction (47%) and gas–stool indiscrimination (34%) [72] (2b). LARS has been used to encompass a wide array of symptoms after sphincter-preserving rectal surgery, including difficulty emptying the bowel, and faecal urgency, clustering and incontinence. The syndrome is poorly

defined [72], but may be stratified by symptom severity into no, minor or major LARS [73] (3b). A meta-analysis of 11 studies found that the estimated prevalence of major LARS was 41% (95% CI 34%–48%) 1 year after SPS for RC [74] (2a). The symptoms usually appear immediately after surgery, develop during the first few months and improve somewhat thereafter, reaching a steady state 1–2 years after surgery, after which further improvement with time is unlikely. The associated impairment has a severe impact on patients' QoL after surgery [75–77] (2b), but also has a specific impact of subscales of HR-QoL such as physical, role, emotional and social functioning, fatigue and diarrhoea [77] (4). The impact and prevalence of LARS are grossly underestimated by most physicians [76, 78] (4).

Radiotherapy (RT), tumour height (anastomotic height) and a preventive ileostomy history are the most frequently assessed variables showing a consistently negative effect on bowel function [74, 79, 80, 81, 82] (2a). Although RT has produced a reduction in the risk of local recurrence, the benefit of RT itself must be balanced against potential toxic damage to the surrounding tissue. A systematic review of late toxicity in RC survivors after RT found that up to 19% of all RC survivors suffer from significant late GI toxicity symptoms that clearly reduce QoL after RT treatment (most commonly diarrhoea, rectal pain, bleeding and incontinence) [80] (2a). Late toxicity tends to occur in tissues with a low cell turnover, such as subcutaneous tissue, fatty tissue and muscle, and within tissues that contain rapidly proliferating cells, such as the wall of the intestine. This means that other unintentionally targeted organs (bladder, genitalia, small intestine) may suffer as well.

The preoperative LARS score (PO-LARS) was developed as a model to predict postoperative bowel function (LARS score) preoperatively; it incorporates key predictive factors for LARS into a nomogram and online tool to individualize patient counselling and aid preoperative consent [83] (2b). The key predictive factors identified in this study were female gender, young age, total mesorectal excision, low tumour height, preventive ileostomy and neoadjuvant RT. When guiding patients preoperatively, PO-LARS may serve as a tool to help patients understand their risk of bowel dysfunction and to identify patients who may require additional postoperative support. Further, major LARS is relatively common in the general population, especially among 50–79-year-olds, which should be considered when guiding patients preoperatively [77, 81] (2b).

Monitoring and evaluation

Two scores, the LARS score and the Memorial Sloan Kettering Cancer Center Bowel Function Instrument (MSK-BFI), were developed specifically to evaluate LARS and may be used to stratify patients based on the severity of their symptoms and to guide therapy [61, 68, 77] (3b). Although the development of both questionnaires was guided by the same purpose they differ significantly in their clinical applicability and scope. Whereas the LARS score is a quick and clinically easy to use tool the MSK-BFI is a more comprehensive instrument that may provide a more in-depth evaluation of LARS [68, 73] (2b). A recent comparative study of the two found that the MSK-BFI and LARS score showed good correlation and had a similar

Bowel dysfunction after rectal cancer

Recommendations

- Rectal cancer survivors should be offered routine screening for bowel dysfunction as major LARS is found in > 40%. High-risk factors are radiotherapy, low tumor height and a history of preventive ileostomy (Grade B).

- Screening for bowel dysfunction should be performed using the validated LARS score (Grade B).

- All survivors with major LARS should be offered treatment, either locally or following referral to a specialized unit (Grade D).

Management strategies

- Ruling out underlying 'organic' lesions that may explain a patient's symptoms after surgery is a prerequisite for treatment (Grade D).

- Objective tests are unnecessary to diagnose LARS (Grade C).

- Soluble fibers (bulking agents) may be beneficial in decreasing clustering and improving stool consistency, provided adequate doses are taken (Grade D).

- Pelvic floor rehabilitation, including pelvic floor muscle training, biofeedback training, and rectal balloon training may improve functional outcome (Grade B).

- Patients with a more severe dysfunction may benefit from transanal irrigation (Grade B).

- Patients with severe refractory symptoms may benefit from sacral nerve stimulation (Grade B).

- Percutaneous tibial nerve stimulation may reduce symptoms of LARS in highly selected patients (Grade B).

- Stoma formation should be reserved for patients with refractory LARS as a final treatment option (Grade D).

FIGURE 4 Guideline recommendations concerning bowel dysfunction in rectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

discriminant validity. They further concluded that, as the LARS score is easier to complete, it may be considered the preferred tool to screen for bowel dysfunction [78] (2b). However, the LARS score may be less useful as an outcome parameter for monitoring treatment effects as its capability to detect changes over time has been questioned [79] (5).

The LARS score is based on the answers to five questions: incontinence for flatus, incontinence for liquid stool, faecal frequency (number of bowel movements per day), clustering of (less than an hour between) bowel movements and urgency. The LARS score does not use a specific recall period, a linear scale or equal-weighting scoring. The response score values are based on the impact of the particular symptom/frequency combination on QoL. The total score is based on the answers to these five questions and ranges from 0 to 42 points. Depending on the total score, patients are classified into three groups: no LARS (0–20), minor LARS [19–25, 80, 81] and major LARS [26–36, 64, 82, 83] (3b). The score has been translated into multiple languages and validated internationally [84] (3b).

The MSK-BFI consists of 18 questions recalling a 4 week timeframe. Fourteen questions are grouped into three subscales, each one of which evaluates an important dimension of bowel function (diet, urgency/soilage and frequency), with four individual questions. The MSK-BFI total score is obtained using a linear scale and an equal-weighting scoring system in which each question has five possible answers ranging from 'never' to 'always', except for one question on the number of bowel movements per 24 h period. The MSK-BFI total

score ranges from 18 to 90 with a score of 90 indicating the best possible bowel function measured with this questionnaire [85] (3b).

Clinical evaluation

Physicians should ensure that ther is no underlying 'organic' lesion that may explain a patient's symptoms after surgery (e.g. radiation-related mucosal lesion, anastomotic stricture, local recurrence). This requires a minimal work-up, with at least digital rectal examination and proctoscopy to exclude anastomotic strictures or recurrence [84] (5).

Objective test methods, such as anorectal manometry and faeco-flowmetry, may also be used. The physician may evaluate postoperative anorectal function based on these tests and suggest appropriate treatment. These tests are not needed to diagnose LARS, but they may be used to monitor the patient's response to treatment [70] (4). Endoanal ultrasonography is not mandatory since it rarely influences the treatment strategy. Evidence of anal sphincter defects will very rarely justify a specific treatment [84] (5). The patient's own rating should be the gold standard, as only the patient can experience the function and perceive its true implications in the context of his or her life (5).

Treatment options

Dietary management. Dietary and behavioral adjustments are common functional self-care strategies for managing bowel dysfunction [85, 86] (4). In a cross-sectional study exploring self-

management and bowel symptoms, patients endorsed fruits and vegetables (cabbage or mustard family greens) as helpful for bowel symptoms (58% and 42.5%, respectively), whereas other vegetables (cabbage, beans, celery, corn, lettuce, onions and spinach) were categorized as troublesome foods by 75.5%. Several foods and food groups were reported as both helpful and troublesome [85] (4).

Very few data exist on dietary management in RC patients. A systematic review of healthy eating interventions in CRC survivors found that the quality of identified studies was variable, with limited evidence to support dietary intervention in CRC survivors due to a lack of robust studies combining all dietary interventions linked to CRC. As a result of the heterogeneity of the studies identified, it was difficult to draw strong conclusions [87] (2a).

Laxatives, constipating agents and medications. Soluble fibres (bulking agents) are well tolerated and may be beneficial in reducing clustering and improving stool consistency provided adequate doses are taken [84] (5). When faecal incontinence is the dominant symptom of LARS, bulking agents with a high-fibre diet and antidiarrhoeal drugs are preferred choices because they can increase anal sphincter tone, leading to improved faecal continence [71] (4).

A RCT investigated the effect of 12 weeks of probiotic administration in CRC survivors. Upon inclusion, patients were screened for IBS according to the ROME III criteria. At baseline, around two thirds of patients in both groups exhibited IBS symptoms, but in the probiotic group the proportion was significantly reduced over the course of the 12 weeks, whereas QoL increased (mental health status and cancer-related fatigue) [52] (1b). Results from long-term follow up are lacking.

Loperamide is one of the most commonly used medications for bowel control, together with sitz bath or local ointments for perianal soreness or itching. Protection of underwear with pads or other absorbents is usually reported. Enemas or lubricating suppositories are also used to optimize incomplete emptying or to plan defaecation [84] (5).

Similar to LARS, urgency and multiple evacuations are frequently seen in patients with diarrhoea-predominant IBS, which is often successfully treated with serotonin receptor antagonists because of their ability to slow gut transit [70] (3a). In a prospective cohort of 25 male patients with complaints of uncontrollable urgency or faecal incontinence following sphincter-preserving resections, Itagaki et al. investigated the efficacy of a daily dose of 5 μg of ramosetron on LARS symptoms and found that it may be efficient in improving urgency, incontinence and bowel frequency [88] (4). Currently, however, ramosetron is not available in Denmark.

Emphasizing the importance of conservative management, Dalsgaard et al. screened 286 patients with the LARS score, of whom 89 had major LARS. Among these, 86 patients requested treatment for their bowel dysfunction and the majority (63%) obtained acceptable function after nurse-led optimized conservative treatment only (17 patients went on to TAI, seven patients were treated with biofeedback, five patients were referred for surgery and three for gastroenterological evaluation). After treatment in the clinic, the prevalence of major LARS declined from 95% to 53% ($p < 0.001$) [89] (4).

Pelvic floor rehabilitation. Pelvic floor rehabilitation, including pelvic floor muscle training, biofeedback training and rectal balloon training, has been accepted as a standard technique for the treatment of faecal incontinence. A 2014 systematic review found that four of five included studies showed that incontinence scores assessed by the Wexner or the modified Cleveland incontinence scores were significantly improved after pelvic floor rehabilitation in RC patients following sphincter-sparing surgery [90] (3a). Supporting this, a recent systematic review including 11 studies of mixed designs found that faecal incontinence was improved in seven studies and bowel frequency decreased in five studies [901] (3a). Specifically, the stool frequency seems to be reduced by biofeedback and pelvic floor muscle training in combination [92] (3a). Overall, the use of pelvic floor rehabilitation seems useful for improving the functional outcome, but the different protocols and durations of training hamper the drawing of solid conclusions [70, 92] (3a).

Transanal irrigation. Increasing evidence suggests that TAI is an effective therapy for selected LARS patients. In a 2010 systematic review by Christensen et al., TAI showed a positive effect in 79%–100% of patients with LARS following surgery for RC [69] (3a). In a study by Martellucci et al., the authors enrolled patients with a rectal resection and postoperative major LARS (LARS score > 30). After 6 months of TAI, the median LARS score declined from 35.1 (range 30–42) to 12.2 (range 0–21; $p < 0.0001$), and at the end of the study, 85% of the patients chose to continue the treatment. Interestingly, benefits of TAI were observed irrespective of early commencement after the closure of diverting ileostomy or after many years of LARS symptoms [93] (2b). In a study by Rosen et al., patients were randomly assigned to TAI and supportive therapy or supportive therapy only after rectal resection and stoma closure regardless of the LARS score or other functional evaluation values. After 12 months of follow-up, >50% of patients continued with TAI, showing a significantly lower number of defaecation episodes per day and per night than the supportive therapy group. However, although the LARS scores were lower in patients who used TAI, the decline failed to reach significance ($p = 0.063$). Evaluation of the Wexner score and the 36-item Short Form Health Survey failed to find any statistically significant difference between TAI and supportive therapy [94] (1b). These results may suggest that patients with a more severe dysfunction may benefit more from the use of TAI, whereas the use of TAI may not be necessary in patients with a less severe dysfunction [95] (5). Patient selection will need to focus on symptom severity but also on the patient's mobility and physical ability to perform TAI on a regular basis. The irrigation process itself needs some training and mental capacity. For this reason, it is mandatory to provide patients with support by experienced staff capable of providing ongoing assistance until the patient is able to perform TAI autonomously [84] (5).

Sacral nerve stimulation/percutaneous tibial nerve stimulation. A 2019 systematic review (including 10 studies) and meta-analysis of the use of sacral nerve stimulation (SNS) in refractory LARS found an overall

median improvement in the scoring system used of 67.0% (range 35.5%–88.2%) after SNS implantation [96](3a). The improvement in LARS was considerable, with a mean reduction of the Cleveland Clinic Incontinence Score and the LARS score by 11.2 points (95% CI 9.4–13.1) and 17.9 points (95% CI 10.2–25.6), respectively [96] (3a). A small case-series evaluating possible predictive factors associated with treatment success found that a direct relationship exists between the height of anastomosis and the LARS score, and the largest LARS score changes (pre–/post-SNS therapy) were found in patients with higher anastomoses, and vice versa [97] (4).

Given the potential risk of infection associated with implantation of a neurostimulator, the less invasive alternative percutaneous tibial nerve stimulation (PTNS) has been proposed [98–100] (1b). Marinello et al. conducted a RCT including 46 patients with severe LARS assigning patients to either PTNS or sham therapy (16 30 min sessions once a week for 12 consecutive weeks, followed by four additional sessions at 2 week intervals over the following 8 weeks). LARS scores were reduced in both groups, but only patients who received PTNS maintained the effect in the long term. The faecal incontinence score was also significantly improved after 12 months in the PTNS group. However, no major changes in either QoL or sexual function were observed in either group [98] (1b).

Stoma. Stoma formation may be proposed to patients with severe LARS with refractory symptoms and impaired HR-QoL as a final treatment option [84] [6].

Stomas in CRC survivors (Figure 5)

Surgery for CRC results in a permanent ostomy in 10%–19% of cases [101, 102] (2a). Several studies have shown that the overall complication rate after ostomy surgery falls in the range of 21%–70%, including late complications such as peristomal dermatitis, parastomal hernia, prolapse and stenosis [102] (2a).

Among CRC survivors with a permanent ostomy, 18%–32% report moderate to severe QoL concerns; however, they have less difficulty adjusting to their ostomies than noncancer ostomates [103, 104] (2a). A systematic review of ostomy-related problems described leakage, skin complications, sexual problems (having a stoma is a predictor of sexual dysfunction) [105] (2a), depressive feelings, gas, constipation, dissatisfaction with appearance, change in clothing, travel difficulties, interference with work and activities, feeling tired and worrying about stomal noises [102] (2a). Survivors spoke of unpredictability when describing the loss of control over the body that resulted from the ostomy. Ostomy function varied daily, causing embarrassment and loss of confidence as leakage, incontinence or flatulence from the ostomy were anticipated [22] (2b). A longitudinal, population-based study found that challenges related to ostomies decrease somewhat over time [106] (3b). In general, however, survivors continue to face challenges related to bowel function, clothing restrictions and dietary adjustments [107] (3b).

Despite the described challenges, a revised 2012 Cochrane review of 35 studies (5127 patients) found insufficient evidence to

Ostomies

Recommendations

- Survivors with a permanent stoma may be offered routine screening for stoma impact on health-related QoL (Grade C).

Management strategies

- Stoma patients should have a life-long open contact to a specialized ostomy nurse (Grade D)
- Stomal irrigation may possibly help patients gain control over bodily functions such as output, gas, and odor (Grade C).
- It is recommended, at peristomal dermatitis is treated by a specialized ostomy nurse (Grade D).
- Foul-smelling flatulence may be treated by enhancement of filters or dietary counseling) (Grade D) or by adding lavender oil to the ostomy bag (Grade C).
- Parastomal hernias/bulging may be managed by using an ostomy hernia belt (Grade D).
- It is recommended that patients with persisting symptoms from parastomal hernias/bulging are referred to a specialized surgical center for evaluation (Grade D).
- Simple prolapse may be managed conservatively by a specialized ostomy nurse (Grade D).
- Stomal stenosis may be conservatively treated with dietary measures (Grade D). In colostomy patients with stenosis, irrigations may be useful (Grade D). If the problem is not resolved, the patient may be referred to a specialized surgical unit for evaluation (Grade D).

FIGURE 5 Guideline recommendations concerning ostomies in colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

allow a firm conclusion to the question of whether the QoL is lower in CRC survivors with or without a stoma [108] (2a). This has subsequently been challenged by larger cross-sectional studies finding that RC survivors with an ostomy reported a significant, clinically relevant poorer physical, role and social functioning and global health status/QoL, poorer body image, more male sexual problems and fewer GI problems than RC survivors without ostomies [45, 109] (2b). A recent systematic review found more conflicting results, with some studies finding that younger patients had inferior HR-QoL compared with older patients, whereas others found no differences. Furthermore, several studies found that both generic and stoma-specific HR-QoL were lower in women than in men [110] (3a).

Attention should be paid to discrepancies in the perception of stoma-related problems and how they impact QoL between healthcare professionals and ostomates [111] (4).

Monitoring and evaluation

The two PROMs most used to evaluate stoma function and QoL are the Modified City of Hope Colorectal Cancer Quality of Life Questionnaire Ostomy (MCOHQOLQO) [109] (3b) and the Stoma QOL questionnaire [111] (3b). In these questionnaires, QoL is calculated as the sum of the scores on several ostomy related items. The MCOHQOLQO has four dimensions (physical well-being, psychological well-being, social well-being and spiritual well-being). The Stoma QoL questionnaire includes 20 items covering four domains – sleep, sexual activity, relations to family and close friends, and social relations to others than family and close friends [111] (3b).

More recently, the Colostomy Impact Score (CIS) was developed to quantify the negative impact on QoL for patients living with an end colostomy. The CIS is weighted to evaluate aspects of colostomy-related problems that have a negative impact on QoL from the patient's point of view. The CIS includes seven items (odour, leakage, stool consistency, pain at the stoma site, skin problems, herniation and stoma management help) with a total range from 0 to 38 points. A score of ≥10 indicates a major colostomy impact [112] (3b). The score has undergone international validation and has been proved reliable, with equal colostomy impact scores between test and retest and an intraclass correlation coefficient in the moderate-to-excellent range [112] (3b).

Challenges in ostomy self-care

A 2018 survey found that nearly two thirds (63%) of respondents reported at least one ostomy self-care challenge. Respondents reported having problems with leakage from the ostomy (28%), skin problems around the ostomy site (26%) and difficulty with ostomy care (22%). More than a quarter reported the need to change their pouching system frequently, whereas 14% needed more than 30 min for ostomy care daily. Younger age and higher BMI were consistently related to ostomy self-care challenges [112] [5].

These same issues were identified in a pooled qualitative analysis by Sun et al. identifying eight prominent themes of stoma self-care issues: bleeding, pain, leakage, skin problems/irritation/rash, wafer-related issues, materials getting under the wafer, time to care for ostomy and solutions to clean the stoma [107] (4).

A close collaboration with specialized ostomy nurses is important as readjustment to change is often necessary [112] (4) and a life-long open contact to a specialized ostomy nurse should be established for all CRC survivors with a permanent ostomy [6].

Colostomy irrigation

Studies report that 16%–30% irrigate their stoma [113] (2b). Positive aspects included controlling output, gas, odour and being able to function with only a sticking plaster over the stoma [107, 113] (4). Negative aspects all related to the time involved in completing the irrigation procedure. Colostomy irrigation involves instillation of 500–1500 ml of tap water into the colon via the stoma to wash out faecal material. This is generally done daily or every 2–3 days, and results in little or no stool evacuation from the stoma until the next irrigation. The procedure takes up to an hour and includes a short (about 6–10 min) instillation period followed by an evacuation lasting up to an hour [113] (4).

Further advice on general ostomy care are available in the ASCN Stoma Care National Guidelines, which can be found at www.asc-nuk.com.

Late complications to ostomy formation

Peristomal dermatitis

Peristomal dermatitis is more common with ileostomy than colostomy and is caused by contact with chemical irritants, mainly effluent from the stoma [114] (2b). Major episodes of peristomal dermatitis are largely a problem for ileostomy patients and it is reported in 5%–25% of patients, but the cumulative long-term risk of developing the condition is an estimated 34% [115] (3a). Severity varies from mild dermatitis to cutaneous necrosis and ulcers. Correct treatment is essential to prevent the vicious circle of peristomal dermatitis and stoma malfunction. Treatment consists of careful cleaning of the skin with water, drying and the application of stoma pastes, powders and protective creams. The diameter of the opening must be adapted to the stoma size. Appliances attached to the skin for 48–72 h must be used to prevent frequent changing. To reduce ileostomy output, dietary recommendations must be established and both fibre and antidiarrhoeal medication must be used. Topical corticosteroids and barrier creams may also be used [116] (5). Performance of a biopsy may be needed to rule out other aetiologies, such as inflammatory bowel disease or malignancy [116] (5). Around 40% of patients with colostomy report skin problems, the most frequent being reddening [103, 107] (2b), typically caused by an inappropriate appliance and aperture, and mechanical issues such as skin stripping.

Parastomal hernia/bulge

Parastomal hernia is one of the most common complications of a colostomy, with a reported incidence for end colostomy and loop colostomy ranging from 4% to 48% and 0% to 30.8%, respectively [114] (3a). Risk factors associated with the development of parastomal hernia are higher body BMI and increasing age [117] (1a). A 2016 cross-sectional study found that, of the 495 operated RC patients with permanent colostomy included in the study, 56 patients developed symptomatic parastomal hernia. Patients with symptoms from their colostomy experienced distress, which highlights the need to reduce all symptoms from the colostomy. Foul-smelling flatulence was the most common symptom (patients with symptomatic parastomal hernia had a 53% higher risk of flatulence), troublesome when loud and/or smelly, along with constipation, diarrhoea and leakage. Authors suggest that enhancements of the filters in the appliances may be a way to alleviate problems related to flatulence. More personalized dietary counselling might be another way [118] (2b). A qualitative study found that the bulge may threaten a patient's ability to manage stoma care and pointed to the importance of easy and swift access to counselling with a stoma care nurse to regain control. To cover the bodily asymmetry and disfigurement, patients found new clothing solutions or used hernia belts or garments [119] (4c). A small RCT exploring the use of essential lavender oil in the colostomy bag found a decrease in the proportion of CRC patients who complained of odour as a problem after 1 month of treatment. No information about the patients' diet was provided in the study [120] (2b). Another study comparing CRC survivors with and without stoma found that, among 336 ostomates, 31.5% had a bulge or a hernia around the stoma, and operation due to parastomal hernia had been performed in 11.7% in the stoma group. Ostomates with a bulge/hernia had significantly more sexual problems and significantly more pain, and the bulge or hernia around the stoma had an additional negative impact on HR-QoL. Stoma-related complaints led to acute medical care in nearly 21% of the stoma patients [121] (2b).

Hernias with mild symptoms may be managed conservatively with an ostomy hernia belt [116] (5). One third of patients will require surgery for complications. Several options are available: local repair, relocation of the stoma and correction with meshes with or without a laparoscopic approach [116] (5).

Prolapse

Prolapse occurs when a proximal segment of the bowel intussuscepts and slides to protrude through the stomal orifice. The prolapsed stoma may cause distress for the patient, but it is usually of no clinical or functional significance. Rarely, prolapse may cause ischaemia or strangulation resulting from excessive oedema of the prolapsed loop. Simple prolapse may be managed by conservative treatment. This should include reassurance for the patient and the fitting of a new stoma appliance [114] (3a). In case of signs of ischaemia or gangrene, surgery is the only treatment option. Surgery may include reversal, if indicated, or refashioning of the new stoma after excising the redundant prolapsed bowel [114] (3a).

Stenosis

Stomal stenosis is reported in 2%–15% of stomas [114] (3a). Stomal stenosis often results in a noisy stoma when flatus is passed, which may be distressing and embarrassing for the patient. Dietary measures may be used for treatment, ensuring that fibre is processed. In colostomy patients, laxatives to maintain soft stool and irrigations may be useful. If the problem is not resolved, the stoma may be reconstructed through laparotomy or laparoscopy. Occasionally, it may be repaired locally by a plasty [116] (5).

Diversion colitis

The surgical interruption of faecal flow may induce inflammation in the nonfunctional region of the distal colon, referred to as diversion colitis (DC). Theoretically, the inflammation typically resolves when the faecal passage resumes. However, a few studies have shown a persisting effect with mucosal and transmural changes in the colon long after reversal of faecal passage [122] (5). The estimated incidence of DC ranges from 70% to 100% [123] (2b). Symptoms of DC include abdominal pain, bleeding, mucous discharge and tenesmus, although many patients do not present with definitive symptoms. The severity of DC is related to diarrhoea after an ileostomy reversal and may adversely affect QoL [123] (2b). A RCT has investigated the use of probiotics in improving bowel function following ileostomy closure but found no difference between active treatment and placebo [124] (1b).

Urinary dysfunction in CRC survivors (Figure 6)

A well-known sequela to treatment for CRC is urinary dysfunction, defined as voiding dysfunction and/or incontinence. The symptoms may be transient and mild, but for others dysfunction is permanent. Posttreatment urinary dysfunction is primarily described in relation to RC survivors with a still unknown incidence due to the broad range reported in the literature (10%–98%). This variability is due mainly to differences in how urinary dysfunction is defined and graded and to differences in patient selection and methods of assessment [45,75,110,125–130] (2a).

A large cross-sectional study on female CRC survivors (5211 patients; colon n = 3533, rectum n = 1678) found that urinary dysfunction had a significant impact on QoL in 18.7% of RC survivors and 14.3% of CC survivors (p < 0.0001) [131] (2b). Similarly, a large cross-sectional study on male CRC survivors (n = 5710; colon n = 3400, rectum n = 2310) found that urinary dysfunction had a significant impact on QoL in 15.8% of RC survivors and 13.6% of CC survivors (p = 0.017) [132] (2b). Rectal resection seems to be an independent risk factor for developing urinary dysfunction with abdominoperineal excision and/or RT increasing the risk even further [110, 129,131–133] (2b). However, one study reported the urinary symptoms induced by RT to affect men only and to be transient [125] (2b). Other risk factors include low tumour height (<5 cm from the anal verge), lymph node involvement, preoperative urinary dysfunction and advanced age [125, 131, 132, 134] (2b).

Urinary dysfunction

Recommendations

- Survivors should be screened routinely for urinary dysfunction as symptoms are present in 10-98% of patients and may affect QoL (Grade B).
- Patients with persisting symptoms > 3-6 months following initial basic treatment should be offered referral for treatment in specialized units (Grade D).

Management strategies

- Using a three-day voiding dairy with registration of fluid intake, voiding episodes, and voided volume in patient with urinary dysfunction is recommended (Grade D).
- The standard of care for urinary dysfunction is conservative management including lifestyle interventions such as moderating fluid intake, avoiding known bladder irritants such as caffeine and alcohol, and smoking cessation (Grade D).
- In postmenopausal women with overactive bladder symptoms and vaginal atrophy, treatment with vaginal estrogens is recommended (Grade D).
- Pelvic floor muscle training with or without biofeedback may alleviate symptoms in stress incontinence (Grade A).
- Sequencing of oral medication should be tailored depending on the most bothersome symptom identified at assessment and includes alpha-blockers and antimuscarinics or mirabegron (Grade D).

FIGURE 6 Guideline recommendations concerning urinary dysfunction in colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

Monitoring and evaluation

Evaluation of patients with postoperative urinary complaints requires consideration of symptoms, severity of complaints and any preexisting urinary dysfunction. Preoperative urinary dysfunction, often due to prostate disease or pelvic floor disorders, is common among patients undergoing treatment for CRC.

The most commonly used PROMs with which to diagnose and monitor urinary dysfunction are listed below. It should be noted that none of these PROMs are validated specifically for assessment of CRC survivors.

The International Prostate Symptom Score (IPSS) was developed for assessment of benign prostatic hyperplasia. It is a validated questionnaire containing seven items, including incomplete bladder emptying, frequency, intermittency, urgency, weak stream, straining and nocturia [133] (3b).

The International Consultation on Incontinence Modular Questionnaire – Male Lower Urinary Tract Symptoms (ICIQ-MLUTS) is validated and covers relevant symptoms regarding both regular urinary tract symptoms and the most prominent symptoms following pelvic surgery [134] (3b). By adding up the prevalence scores of the individual items, a voiding symptoms subscale (0–20) and an incontinence symptoms subscale (0–24) can be calculated. There is, however, no defined cut-off point for good versus poor function nor a definition of a clinically relevant difference. The same score is available for female patients [the female version is the International Consultation on Incontinence Modular Questionnaire – Female Lower Urinary Tract Symptoms (ICIQ-FLUTS)] [135] (3b).

Assessment

General assessment of posttreatment urinary dysfunction includes self-reported incontinence, PROMs and a 3-day voiding dairy with registration of fluid intake, voiding episodes, voided volume and a pad test. Moreover, dipstick urinalysis is employed for leucocytes and nitrites to rule out infection and haematuria. Additional uroflow rate and bladder ultrasound for identifying residual urine may be useful [135] (5). In men, it is important to keep in mind that the prevalence of lower urinary tract symptoms increases with age, and new lower urinary tract symptoms may be indicative of prostate hyperplasia or cancer and physical examination should include a prostate exam [135] [6]. In women, gynaecological examination is recommended to evaluate pelvic organ prolapse and/or vaginal atrophy [135] (5).

Treatment

Evidence-based management of urological dysfunction in CRC survivors is lacking. Although several treatments for urological symptoms are available, the evidence is insufficient to support their

effectiveness in CRC survivors. Recommendations are thus based on indirect evidence (grade D).

Urinary incontinence may be divided into stress, urge and overflow incontinence. Regardless of subtype, initial treatment should consist of behavioural modification, which includes moderating fluid intake, avoiding known bladder irritants such as caffeine and alcohol, and smoking cessation. Use of pads and collecting devices (body-worn urinals) is possible but should be temporary until proper management concerning the urinary incontinence has been initiated. Use could also be permanent if the patient is satisfied with the device or is not a candidate for further treatment due to comorbidity [135, 136](5). A small prospective series in 45 RC survivors (29 men) showed great reversibility in urinary incontinence (stress incontinence) after early initiation of pelvic floor muscle exercise [127] (2b). Moreover, concomitant biofeedback could synergistically reinforce the pelvic floor muscle exercise [137] (1b). Another first-line treatment option is bladder training, wherein scheduled voiding is used to eliminate pollakiuria and/or urinary incontinence [138] (5).

Pharmacological options are available as second-line therapy. Oral medication is centred on the use of alpha-blockers and antimuscarinics/mirabegron (beta-3 agonist). Sequencing of medication should be tailored according to the most bothersome symptom identified upon assessment. Alpha-blockers may be used in the case of compromised bladder emptying. Antimuscarinics/mirabegron may be used to treat urgency and incontinence (overactive bladder) as they relax smooth muscles [129, 135] (2a). The European Association of Urology guidelines recommend initiating antimuscarinics in case of urgency urine incontinence [139] (1b). In postmenopausal women, vaginal oestrogen treatment has been shown to improve overactive bladder symptoms and is recommended as initial treatment, particularly if other symptoms of vulvovaginal atrophy are present [140] (1a).

The treatment options for urinary retention and resultant overflow incontinence are limited. No pharmacological options have been approved that may increase bladder contractility in the setting of urinary retention. Clean intermittent catheterization, done either by the patient or a caretaker, is a common technique used to facilitate regular bladder emptying, thereby avoiding overflow [129] (5). If intermittent catheterization is not possible, the patients may have a urethral or a suprapubic catheter.

Sexual dysfunction in CRC survivors (Figure 7)

Sexual well-being is a significant health and QoL issue in cancer survivorship. The term 'sexual dysfunction' is poorly defined, and the term is inconsistent across comparative literature. It includes both physical and psychological factors. Significant heterogeneity in the prevalence of sexual dysfunction following treatment for CRC is reported in the literature with rates ranging from 5% to 93% [110, 125, 141–143] (2a).

RC survivors report a higher alteration of sexual desire and more difficulty reaching an orgasm than CC survivors [141, 144](2b). Also,

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Sexual dysfunction

Recommendations

- Survivors should be offered routine screening for sexual dysfunction as this affects up to 93% of men and 88% of women (Grade B).

- Sexual function in survivors requires focused assessment beyond broad QoL evaluation (Grade D). Attention should be paid to the fact that radiotherapy, stoma formation, and bowel dysfunction are associated with an increased risk of sexual dysfunction.

- Patients with persisting symptoms should be offered referral for treatment in specialized units (Grade D).

Management strategies

- Sex hormones in survivors with relevant complaints should be measured and replacement therapy considered, if needed (Grade B).

- Data suggest that the timing of penile rehabilitation is important and that early initiation of penile rehabilitation after injury yields improved outcomes (Grade D).

- Male patients with erectile dysfunction shall be offered treatment with oral phosphodiesterase type-5 inhibitors (Grade A).

- In female survivors with sexual dysfunction, psychoeducational interventions have shown promising results (Grade B).

- It is recommended to offer hormone replacement therapy ± vaginal estrogens to women with treatment-induced menopause and superficial dyspareunia (Grade D).

- Introital- or vaginal fibrosis and/or deep dyspareunia should be treated with vaginal dilation (Grade B).

FIGURE 7 Guideline recommendations concerning sexual dysfunction in colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

having a stoma is a predictor of sexual dysfunction with a strong level of evidence [105] (2b). Studies have found that bowel dysfunction is associated with a lack of sexual desire, sexual inactivity and sexual dissatisfaction. Specifically, faecal incontinence has a significant impact on sexuality (desire, frequency of intercourse, reaching orgasm and satisfaction with hugging and kissing) [110, 141, 145] (2b). In a case–control study, CRC survivors with ostomy were more anxious than healthy volunteers, and a low frequency of sexual intercourse was significantly more common in this patient group (68% vs. 30%), with 54% avoiding intercourse compared with 4% among controls [146] (3b).

Sexual dysfunction in men

Male sexual dysfunction is reported in up to 93% of CRC survivors [143] (4) and is defined as the inability to achieve a satisfactory sexual relationship, which may involve inadequacy of erection (erectile dysfunction, ED) or problems with ejaculation (ejaculatory dysfunction, EJD). However, male sexual dysfunction as a late TRS after CRC may also include penile shortening, penile curvature, dysorgasmia and/or other ejaculatory disorders including retrograde ejaculation, loss of or alterations in ejaculation, urine leakage at the time of orgasm (climacturia), azoospermia and low testosterone levels caused by scrotal radiation [141, 144] (2a).

ED or impotence is defined as the persistent inability to attain and maintain an erection sufficient to permit satisfactory sexual performance and is reported in 11%–93% of CRC survivors [143–145, 147–150] (2b), whereas EJD is reported in 19%–68% [144, 145, 148] (2b).

Cross-sectional studies have found that RC survivors have significantly more problems with ED than CC survivors [144, 151] (2b) and that both a stoma and the use of RT were independent risk factors for developing ED [150, 151] (2b). It is important to remember that the incidence of male sexual dysfunction increases with age and is common in the general population [152] (3a).

In RC patients also treated with RT the testes may be exposed to direct and/or scattered radiation. A systematic review of men exposed to long-course RT during RC treatment found an increased risk of developing testicular dysfunction with decreased serum testosterone levels compared with both pretreatment values and with men treated with surgery alone [153] (2a).

Monitoring and evaluation

For most patients, sexual dysfunction is a private matter and therefore they will not speak frankly about this unless asked directly. Hence, it is of outmost importance to screen and monitor function following treatment.

The EORTC QoL CRC questionnaire module (QLQ-CR38 (29)) consists of 38 (29) items including items on body image and sexuality. Over the years, several instruments for monitoring of sexual function have been developed (Table 1).

PROM specifically for male patients

The most widely used PROM for evaluating sexual function in men is the International Index of Erectile Function (IIEF), although it must be noted that the IIEF score was not specifically developed and validated for postsurgery ED [103] (2a). The IIEF is a validated, multidimensional, self-administered questionnaire comprising five domains: erectile function, orgasmic function, intercourse satisfaction, sexual desire and overall satisfaction. Each domain has a maximum score of 30, 10, 10, 15 and 10 points, respectively, and a minimum score of 1, 0, 2, 0 and 2, respectively [154] (3b).

Treatment options

The most common management strategies for ED include psychological evaluation and support, pharmacological therapies and mechanical treatments (e.g. vacuum erection devices and penile prosthesis implantation). Medical treatments comprise oral administration of phosphodiesterase type-5 inhibitors (PDE-5is) and the direct drug delivery of prostaglandins via topical creams, intraurethral suppositories or intracavernosal injections [154] (1a). Oral PDE-5is are currently considered the first-line therapy for ED as a recent systematic review of RCTs concluded that despite the limited evidence available in the literature, the oral administration of PDE-5is appears to improve IIEF score, especially in the short term, in male patients diagnosed with ED after rectal surgery [154] (1a). The literature lacks long-term studies (follow-up >12 months) on important treatment efficacy parameters such as the response rate, dose adjustment and patient satisfaction over time.

In the treatment of patients undergoing radical prostatectomy, penile rehabilitation is defined as the use of any device, pharmacological agent or intervention to promote male sexual function (including girth, length, curvature and quality and longevity of tumescence) before and after any insult to the penile erectile physiological axis. Data suggest that the timing of penile rehabilitation is important, with an early initiation after injury yielding improved outcomes [155] (5).

Vacuum erection devices (VEDs) are progressively being used as part of the treatment regimen in penile rehabilitation following radical prostatectomy. Due to the mechanism of action of VEDs they may improve erectile function regardless of the underlying pathology [155] (5). However, the use of the device has not formally been investigated in CRC survivors.

Prostaglandin E1 may be administered in two ways; as an intracavernosal injection or as an intra-urethral suppository. Current guidelines from the American Urological Association only recommend the use of prostaglandins in select patients who are either not candidates for or have failed therapy with oral PDE-5is.

Sex hormones in radiated RC patients with relevant complaints should be measured as testosterone levels <8 nmol/L may precipitate specific symptoms caused by testosterone deficiency such as impaired physical, psychological and sexual function after treatment [153] (2a).

Sexual dysfunction in women

Sexual dysfunction has been reported in up to 88% of female CRC survivors [143, 156, 157] (2b). A clinical definition of female sexual dysfunction is the persistent/recurring decrease in sexual desire, the difficulty/inability to achieve an orgasm and/or pain during sexual intercourse. However, sexual dysfunction in women covers a broad spectrum of symptoms also including impairment of one's typical pattern of intimate sexual response, changes in sexual desire and arousal, pain, lack of femininity, sexual attractiveness and confidence [157] (3a). It is important to bear in mind that different aspects of sexual dysfunction are common in the general population and were reported in up to 70%–80% of 55–74-year-old women [158] (3a). The association between sexual/relationship satisfaction and measures of psychological well-being is consistent and strong [159, 160] (2b).

A recent large cross-sectional study including 2402 female CRC survivors found that, overall, female RC survivors reported more sexual inactivity and problems than female CC survivors, but no differences were observed in any sexual function domains when excluding irradiated patients and patients with a permanent stoma [161] (2b). A systematic review by Canty et al. found that among female CRC survivors not engaging in sexual activities posttreatment, the main reason was a physical issue making sexual activity difficult or uncomfortable [157] (3a). Dyspareunia is found among 36%–60% and decreased lubrication/vaginal dryness in 67%–72% of female CRC survivors [123, 159, 160] (2a). A permanent stoma is associated with sexual inactivity and overall sexual dysfunction [162] (2b). Canty et al., however, found that having a stoma did not directly affect sexual desire or function, but that women worried about their partner's response to the stoma or about leakage during intimacy [163] (3a).

In RC survivors, RT exposure increases the odds for overall sexual dysfunction and is associated with dyspareunia [162] (2b). Compared with patients who had surgery only, preoperative RT had a negative effect on sexual functioning (sexual interest, pleasure and satisfaction), whereas a similar level of vaginal dryness and dyspareunia was found across treatments [157, 164] (2a). RT induces a loss of vaginal epithelium, usually resolving within 3–6 months posttreatment but, histologically, the new epithelium is different from normal epithelium [148] (5). The addition of chemotherapy may cause amenorrhoea, weight changes, hair loss and fatigue, thereby impairing the sexual response and reducing motivation to engage in sexual activity [148] (5).

Premature iatrogenic menopause secondary to chemo- and/or radiotherapy may cause infertility, mood disorders (depression, loss of self-esteem, relational difficulties), disorders secondary to the oestrogenic loss (hot flashes, insomnia, memory difficulties, vaginal dryness, joint pain, osteopenia/osteoporosis) and disorders secondary to the androgenic loss (loss of sexual interest, orgasmic difficulties, fatigue, loss of assertiveness) [165] (4).

Monitoring and evaluation

Basing sexual well-being outcomes on measures primarily focused on genital function, sexual response cycle and heteronormative penetrative intercourse may miss important aspects of women's intimate relationships with their partners.

The most used PROM for evaluating female sexual function is the Female Sexual Function Index (IFSF) [103] (2a), a 19-item questionnaire assessing key dimensions of female sexual function. It was developed for healthy patients and does not consider cancer-related symptoms such as vaginal dimension or bleeding and is therefore not relevant in this population [165] (3b).

The Sexual Function Vaginal Changes questionnaire (SVQ) is a 17-item instrument that addresses the key dimensions of female sexual dysfunction and vaginal problems in patients with gynaecological cancer, with specific questions on vaginal dimension and bleeding. Hence, it has been found to be useful in female CRC survivors. However, it does not take into consideration the impact on QoL. It was originally developed and validated in Danish patients [166] (3b).

The Rectal Cancer Female Sexuality Score was developed specifically for female RC survivors. The score includes seven items with weighted scoring values based directly on QoL impact. The values are added to yield a total score ranging from 0 to 29 points. A score ≥9 indicates sexual dysfunction. The score has a sensitivity/specificity of 76%/75% for detecting patients bothered by sexual dysfunction with a negative QoL impact [158] (3b).

Treatment options

To enhance intimacy, it is essential to evaluate the patient's specific sexual concerns and to efficiently address the patient's worry and distress. A systematic review exploring interventions to improve sexual well-being among female pelvic cancer survivors found that sexual distress and intimacy were correlated with sexual communication. Sexual distress, sexual communication and intimacy were significantly associated with self-efficacy: self-efficacy to communicate effectively about issues related to physical intimacy or sex, self-efficacy to deal effectively with sexual difficulties and self-efficacy to enjoy intimacy despite physical limitations [166] (3a). Psychoeducational interventions have thus shown promising results [157, 167] (1b).

Sexual pain difficulties in women are predominantly associated with vaginal dryness, vaginal stenosis and dyspareunia. The most effective management for superficial dyspareunia in women with treatment-induced menopause is the prompt offer of hormone replacement therapy and, where appropriate, vaginal oestrogens [168] (2b). If contraindicated, nonhormonal vaginal moisturizers may be used. Furthermore, most women will need to use an intimate lubricant (water-, oil- or silicone-based) to reduce the friction associated with penetrative sexual intercourse or vulval contact.

Sex hormones in radiated RC survivors with relevant complaints should be measured and replacement therapy considered as needed [165] (4). For women with introital or vaginal fibrosis and/or deep dyspareunia after radiotherapy, vaginal dilation is recommended. A systematic Cochrane review by Denton et al. found that evidence is sufficient to endorse widespread use of vaginal dilators [169] (2a). A prospective intervention study in female pelvic cancer survivors found that when introducing vaginal dilators of increasing sizes three times weekly after concluding RT treatment, 63% of patients

were able to return to the pre-RT size at 6 and 12 months [170] (3b). However, a lack of evidence exists on the optimal timing, frequency and duration of vaginal dilator use.

Pain and chemotherapy-induced neuropathy in CRC survivors (Figure 8)

Pain assessment and treatment of cancer-related pain in general are beyond the scope of this guideline, and we refer to other publications on the subject. In this guideline, we focus on pain related to side effects from treatments specific to CRC.

Prolonged pelvic pain is defined as pain that has persisted for more than 6 months. Cancer-related pain may originate from any of the organs of the pelvis and arise after cancer treatment. Prolonged pain may, via various mechanisms in the nervous system, lead to altered function and various symptoms/discomfort of the skin, bladder, muscles, intestines and gynaecological organs [171] (3a).

A cohort study on opioid use in CC survivors (n = 2039) showed an increased use of opioids after diagnosis. Most survivors were treated with surgery alone, 13.6% received concomitant chemotherapy and 1.5% RT. Administration of chemotherapy was related to an increased risk of pain [172] (2b).

A recent systematic review on late (>3 months) GI toxicity after treatment for RC reported rectal pain in 13% of patients. Further, a trend towards increased rectal pain was shown in patients treated with RT and surgery compared with surgery alone. Furthermore, an increased toxicity with chemoradiotherapy was recorded compared with RT alone, although this was not significant [80] (3a).

In a previous Danish study including 1369 RC patients, 31% reported chronic pain in the pelvic area or lower extremities and 13%

experienced pain daily. Pain was associated with female gender, type of surgery, (chemo-)radiotherapy and young age, all of which impacted patients' QoL [173] (2b). Among 100 CRC survivors (diagnosis 1–10 years previously) selected for a telephone survey, 23% reported chronic pain and 39% found pain to be related to their cancer treatment [174] (2b). In CRC survivors, pain was found to be multifactorial, including comorbidities, age and gender besides oncological treatments [174, 175] (2b). Pain was related to several aspects of CRC survivorship including a poorer self-related health and overall QoL [16, 176] (2b).

Screening for pelvic pain may be done using a validated short form RC pain score [175] (3b).

Evidence-based pain rehabilitation programmes, available through referral in most regions, focus on learning to manage and live with pain as a long-term condition if no specific therapy is available.

Specific causes of treatment-related pain in CRC, pelvic insufficiency fracture (PIF) and chemotherapy-induced peripheral neuropathy (CIPN), will be addressed in the following.

Chemotherapy-induced peripheral neuropathy

CIPN is a well-known side effect to certain types of chemotherapy. Oxaliplatin used in CRC causes chronic neuropathy, which is dose dependent and correlated with the cumulative dose of oxaliplatin [177, 178] (2b). Symptoms have a characteristic 'glove-and-stocking-like' distribution and include sensory loss, paraesthesia, dysaesthesia and pain [152, 179] (2b). A study including 406 patients found the prevalence of CIPN to be 31.3%, and a third of these patients (36.5%) also had neuropathic pain [180] (2b). This finding is supported by a Danish study in which a third of patients with symptoms

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Pain and chemotherapy-induced neuropathy

Recommendations

- It is recommended that survivors with persisting pain should undergo diagnostic work up to determine the cause of their pain (Grade D).
- It is recommended that survivors treated with oxaliplatin should be screened for CIPN (Grade D).

Management strategies

- Duloxetine reduces pain in painful CIPN (Grade A).
- Agents recommended for the treatment of neuropathic pain may be effective in the treatment of painful CIPN (Grade D).
- MRI should be the preferred imaging modality for detecting pelvic insufficiency fractures (Grade B).
- Consider treatment with calcium and vitamin D in case of radiotherapy (Grade D).

FIGURE 8 Guideline recommendations concerning pain and chemotherapy induced peripheral neuropathy (CIPN) in colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

of neuropathy reported neuropathic pain 5 years after treatment with oxaliplatin [181] (2b). Both studies concluded that little improvement in CIPN occurred from 1 year until 5 years after chemotherapy. Sensory symptoms in the lower extremities are a prominent late sequela after treatment with oxaliplatin, and several studies have found that chronic CIPN has a negative influence on QoL [152, 180, 181] (2b). One study suggested that the negative influence on QoL is only related to painful CIPN, since no difference was found in QoL of survivors with nonpainful CIPN and survivors without CIPN. Patients with high CIPN (upper 30% of scores in the EORTC QLQ-CIPN20) also reported more anxiety and depressive symptoms and more fatigue than patients with a low CIPN. However, the relationship between CIPN and fatigue is possibly mediated by both anxiety and depression [182] (2b).

Risk factors for CIPN have been discussed in several studies. However, agreement is limited. A study including 3607 patients aged >65 years found that the incidence of oxaliplatin-induced CIPN increased with advancing age and, specifically, was greater among patients aged >70 years [163] (2b). In contrast, another study in 406 patients found no correlation between age and CIPN [180] (2b). A systematic review and meta-analysis addressed the question of risk factors. None of the suggested risk factors including baseline neuropathy, smoking and decreased creatinine clearance were verified in new population-based datasets. Even so, sensory changes during oxaliplatin treatment, including cold allodynia and cold hyperalgesia, have previously been documented as predictors of CIPN [183] (3a).

Monitoring and evaluation

A systematic review and Delphi survey published in 2017 concluded that a consensus 'gold standard' clinical assessment including PRO and clinician input has yet to be established [184] (2a). However, several PRO screening tools, with different objectives, have been investigated and validated [162, 185–189] (2b).

One of the widely used clinical tools for detecting neuropathy during chemotherapy is the National Cancer Institute – Common Terminology Criteria for Adverse Events (NCICTCAE), but several studies have found that this instrument is not sensitive to change and has significant inter-rater variability [162, 186] (3a).

In the case of painful CIPN, the standard approach to neuropathic pain, the NeuPSIG guidelines for assessment and diagnosis of neuropathic pain may be applied. These guidelines recommend both using screening questionnaires to identify potential patients and using clinical examination as an important part of the assessment. The clinical examinations will typically consist of nerve conduction studies, quantitative sensory testing, and examination of intraepidermal nerve fiber density (IENFD). This is challenging in a non-specialist setting, particularly when using more detailed sensory profiling for the definitive diagnosis, and referral to a specialist is therefore recommended [190] (5).

Treatment options

In 2020, The American Society of Clinical Oncology (ASCO) published a guideline update on the prevention and management of CIPN [8] (1a). No agents were found to be effective in the prevention of CIPN [8] (1a). Instead, clinicians were recommended to assess the appropriateness of dose delaying, dose reduction, substitutions or discontinuation of chemotherapy in patients who develop intolerable neuropathy.

In patients with chronic CIPN, distinguishing between painful and non-painful CIPN is important. No agents have been found to be effective in non-painful CIPN. Duloxetine is one of the few agents for which a positive RCT exists for painful CIPN [191] (1b). Therefore, duloxetine is the only agent recommended in the ASCO guidelines. However, it is important to notice that the numbers needed to treat are high for serotonin–noradrenaline reuptake inhibitors and treatment can induce significant side-effects, with cognitive and gastrointestinal side effects being the most frequent [190].

A lack of good quality clinical trials exists focusing on treatment of established painful CIPN. A review published in 2017 found that only seven published RCTs tested the efficacy of treatments for CIPN. Moreover, the trials that evaluated the efficacy of neuropathic pain treatments typically did not evaluated pain but general peripheral neuropathy symptoms, including dysesthaesias and paraesthesia [192] (2a). Based on efficacy in other neuropathic pain syndromes, and the fact that sensory phenotypes in patients with CIPN is very similar to those seen in patients with HIV and mixed polyneuropathy, other agents recommended for the treatment of neuropathic pain in the (NeuPSIG) treatment guidelines, i.e., amitriptyline, pregabalin, gabapentin, and nortriptyline, may be trialed ([193, 194], Ventzel et al. 2018) (1a).

Pelvic insufficiency fracture

PIF is a well-known late side effect after pelvic chemoradiotherapy that may cause pain and decreased mobility [195] (3a). PIFs are described in 3.1%–33% of RC patients after chemoradiotherapy or RT [195-202] (1b) but are best documented after radiation for gynaecological cancers [203] (2a). Studies on PIFs after RT or chemoradiotherapy in RC have mainly been retrospective and characterized by heterogeneity with respect to definition, timing, imaging methods, RT techniques and follow-up [195] (3a). Imaging method is important, as MRI is estimated to have a sensitivity of 99%–100% and a specificity of 85% for stress fractures in general and was found to be superior to CT (sensitivity 69%) in the pelvic/femoral area [204, 205] (3b). In RC survivors, no systematic reviews or meta-analyses exist on PIF. In gynaecological cancer, two large studies (systematic reviews and meta-analyses) on PIF after RT ($n = 3929$ and $n = 6488$) found PIF incidences of 9.4% and 14% detected a median of 8–39 and 7.1–19 months after RT, respectively [203, 206] (2a). The most frequently found risk factors across the included studies were advanced age, postmenopausal status, low BMI and osteoporosis, older RT treatment techniques and higher RT doses [203] (2a). The most frequent

localization was the sacral body/near the sacroiliac joint (60%–73.6%) followed by the pubic bones (12%–13%). The ratio of symptomatic patients differed, but was generally around 50%–60% [203] (2a). These data are not directly applicable to the field of RC as the radiation dose, techniques and chemotherapy are different. However, fracture sites predominantly in weight-bearing areas, relation to higher radiation doses, association with increasing age and postmenopausal status were also found in RC [195, 201, 202, 207] (2b).

Studies on treatment and preventive measures for PIFs are lacking. The ESMO 2020 guidelines on bone health in cancer do not specifically address chemoradiotherapy- or RT-induced PIFs. However, the guidelines state that 'all patients receiving treatments that are known to adversely affect bone health should be advised to consume a calcium enriched diet (or supplement), exercise moderately, and take 1000–2000 IU vitamin D3 every day' [208] (5).

In a 2020 systematic review on gynaecological patients, information on treatment of PIFs was available for 456 patients. Conservative treatment was applied in 84.6% of cases (analgesics, bed rest and observation), hospitalization or surgery in 9.4%, and bone-directed therapies were used in 6% of cases (bisphosphonates, calcium, vitamin D and hormone replacement therapy) [203] (2a). A Cochrane review on pharmacological interventions for the prevention of PIF associated with pelvic RT has been conducted [209] (1a). Two RCTs were included, both in men undergoing pelvic RT and hormone replacement therapy for prostate cancer. The review concluded that evidence is insufficient to support that zoledronic acid and other medicines are sufficient to prevent radiation-induced bone complications.

Cancer-related fatigue in CRC survivors (Figure 9)

Cancer-related fatigue (CRF) is a potential long-term effect of treatment that is prevalent among cancer survivors and often causes significant disruption in functioning and reduces QoL [2, 210] (2a). The European Association for Palliative Care offers a working definition of CRF as 'a subjective feeling of tiredness, weakness or lack of energy'. The NCCN defines cancer-related fatigue as 'a distressing, persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual function'.

CRF is a common symptom in CRC survivors, and clinically relevant fatigue is reported among 56%–67% of long-term survivors [33, 211] (2b). A 2020 systematic review and meta-analysis of the symptom experience in CRC survivors found that among 10 postcancer treatment symptoms analysed, fatigue was rated the most severe by patients [47] (2a). Greater fatigue was associated with a lower mental QoL and a lower physical QoL [211] (2b).

Monitoring and evaluation

The high prevalence of moderate to severe CRF in survivors warrants routine screening, assessment and management of patient-reported fatigue. For patients who report moderate to severe fatigue, a comprehensive assessment should be conducted, and medical and treatable contributing factors should be addressed [2] (2a).

Tools that are specific to fatigue assessment in patients include the Multidimensional Fatigue Symptom Inventory (MFSI), the Multidimensional Fatigue Inventory (MFI-20), the Piper Fatigue Scale and the Visual Analogue Scale to Evaluate Fatigue Severity (VASF), as well as those that specifically measure CRF [the Functional Assessment of Cancer Therapy Fatigue Instrument (FACIT-F) and the Schwartz Cancer Fatigue Scale] [206] (5).

Clinical assessment

A detailed laboratory assessment should be performed for differential diagnosis of fatigue, including indicators of anaemia, electrolyte dysregulation, organ dysfunction, hypothyroidism, infection, hormone imbalance and vitamin deficiency [212] (5).

Cancer-related fatigue

Recommendations

- Survivors should be offered routine screening for cancer-related fatigue as this is a common symptom, which is rated the most severe by patients (Grade B).

Management strategies

- Relevant laboratory assessment for differential diagnostics of fatigue is recommended (Grade D).
- Physical activity may improve cancer-related fatigue, but conclusive evidence is lacking (Grade B).

FIGURE 9 Guideline recommendations concerning cancer-related fatigue in colorectal cancer survivors. Recommendations marked A are the strongest whereas recommendations marked D are the weakest according to the Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations. Recommendations are of a more general character whereas management strategies provide more practical advice suited for initiation on site before referral to specialized units.

Treatment options

Most patients with fatigue will require symptomatic treatment using a combination of pharmacological and nonpharmacological approaches. For example, the following may help reduce fatigue: correcting anaemia and electrolyte disturbances, managing comorbidities, alleviating pain, emotional distress and sleep disturbances, and addressing dehydration [212] (5). Evidence is limited to support the use of psychostimulants in the management of fatigue among patients who are disease-free after active treatment [2] (2a).

If fatigue seems to arise as a side effect of the therapy provided, physical activity is known to produce numerous beneficial physiological changes in markers of physical performance, which may help to counter some of the causes of fatigue, such as increasing haemoglobin levels, cardiorespiratory fitness and capacity, muscle mass and strength [213] (2b). In a 2018 systematic review of the effect of physical activity on fatigue among CRC survivors, a meta-analysis of the RCTs failed to show that physical activity had a significant effect on fatigue. However, reduced levels of fatigue were observed in all studies. A possible explanation why the meta-analysis failed to establish an effect is that none of the included trials were conducted specifically among fatigued survivors [214] (1b).

A cross-sectional analysis by the associations of the dietary World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) found that a higher vegetable intake (per 50 g) was associated with an improved global QoL, improved physical functioning and lower levels of fatigue in CRC survivors [214] (3b).

LIMITATIONS

The chosen symptom categories have been identified based on the available literature and the experience of the participating expert panel. Other TRS of cancer treatment less specific for CRC survivors are not covered here. Most studies are limited by sample size (single centre) and design (cross-sectional, small retrospective cohort studies).

CONCLUSION

QoL and late TRS should be monitored systematically in CRC survivors to identify patients who require further treatment or specialist evaluation or support. This guideline was developed to support clinical decision-making and to promote evidence-based treatment and quality improvement. An increased awareness and acceptance of the extent of the problem can stimulate and facilitate the multidisciplinary collaboration which is often necessary to manage these problems as well as to generate much needed evidence-based treatment algorithms.

AUTHOR CONTRIBUTIONS

Haas S: Investigation; Writing - original draft; Methodology; Validation; Writing - review & editing. **Mikkelsen AH:** Investigation; Methodology; Validation; Writing - review - & editing. **Kronborg CJS:** Investigation; Writing - original draft; Methodology; Validation; Writing - review & editing. **Oggesen BT:** Investigation; Methodology; Validation; Writing - review & editing. **Møller PF:** Investigation; Validation; Methodology; Writing - review - & editing. **Fassov J:** Investigation; Writing - original draft; Methodology; Validation; Writing - review & editing. **Frederiksen NA:** Investigation; Methodology; Validation; Writing - review & editing. **Krogsgaard M:** Investigation; Writing - original draft; Methodology; Validation. **Graugaard-Jensen C:** Investigation; Methodology; Validation; Writing - review & editing. **Ventzel L[10]:** Investigation; Writing - original draft; Methodology; Validation; Writing - review & editing. **Christensen P:** Conceptualization; Investigation; Funding acquisition; Methodology; Validation; Writing - review & editing; Supervision. **Emmertsen KJ:** Conceptualization; Investigation; Funding acquisition; Writing - original draft; Methodology; Validation; Writing - review & editing; Project administration; Supervision.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethics approval, patient consent and clinical trial registration are not applicable/not relevant.

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