European Journal of Cancer 130 (2020) 102–113

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Diagnosing deficits in quality of life and providing tailored therapeutic options: Results of a randomised trial in 220 patients with colorectal cancer☆

Monika Klinkhammer-Schalke [a,*], Brunhilde Steinger [a], Michael Koller [b], Florian Zeman [b], Alois Fürst [c], Julia Gumpp [d], Robert Obermaier [e], Pompiliu Piso [f], Patricia Lindberg-Scharf [a] for the Regensburg QoL Study Group[1]

[a] *Tumor Center Regensburg, Institute of Quality Management and Health Services Research of the University of Regensburg, Am Biopark 9, 93053 Regensburg, Germany*
[b] *Center for Clinical Studies, University Hospital Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany*
[c] *Caritas-Hospital St. Josef, Department of Surgery, Landshuter Str. 65, 93053 Regensburg, Germany*
[d] *Klinikum Neumarkt, Department of Surgery, Nürnberger Str. 12, 92318 Neumarkt, Germany*
[e] *Klinikum St. Elisabeth Straubing, Department of Surgery, St.-Elisabeth-Straße 23, 94315 Straubing, Germany*
[f] *Hospital Barmherzige Brüder Regensburg, Department of Surgery, Prüfeninger Str. 86, 93049 Regensburg, Germany*

Received 30 October 2019; received in revised form 9 January 2020; accepted 23 January 2020
Available online 13 March 2020

KEYWORDS
Quality of life;
Colorectal cancer;
Definitive RCT;
Complex intervention;
Effectiveness of quality of life implementation

Abstract ***Background:*** The implementation of quality of life (QoL) concepts in routine care, is still an open matter. We followed the Medical Research Council framework for complex interventions to implement a model of QoL diagnosis and therapeutic options, and investigated its effectiveness in patients with colorectal cancer.
Methods: This randomised, single-blind, multicentre, clinical trial enrolled patients diagnosed with primary colorectal cancer aged 18 years or older who were surgically treated in one of four recruiting hospitals in Germany. All patients received aftercare from one of 178 coordinating practitioners (CPs) who had access to 75 healthcare professionals providing tailored therapies. QoL was measured (EORTC QLQ-C30, QLQ-CR29) in all patients after surgery (baseline) and during aftercare (3, 6, 12, 18 months). Patients were randomised (1:1) into two groups: a care pathway, including QoL-profiles consisting of 13 QoL scales plus specific therapeutic recommendations forwarded to the patient's CP or standard postoperative care

☆ Prior presentation: Presented at the Annual Meeting of the American Society of Clinical Oncology, Chicago, IL, June 1–5, 2018.

* *Corresponding author*: Tumor Center Regensburg, Institute of Quality Management and Health Services Research, University of Regensburg, Am Biopark 9, 93053 Regensburg, Germany.
E-mail address: monika.klinkhammer-schalke@ur.de (M. Klinkhammer-Schalke).

[1] The members of the collabration group "Regensburg QoL Study Group" are listed in Appendix.

https://doi.org/10.1016/j.ejca.2020.01.025

adhering to the German national guideline for colorectal cancer (control). The primary endpoint was the proportion of patients in each group with a need for QoL therapy 12 months after surgery. Analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, number NCT02321813 and closed to accrual.

Findings: Between Jan 13, 2014, and Oct 28, 2015, 220 patients were enrolled and randomly assigned (n = 110 per group). At baseline (in hospital after surgery), a need for QoL therapy was diagnosed in 92/103 (89%) of intervention and 86/104 (83%) of control group patients. At 12 months (primary endpoint) the proportion of patients with a need for QoL therapy was 35/83 (42%; 95% CI 31–54%) in the intervention group versus 50/87 (57%; 95% CI: 46–68%) in the control group (p = 0·046, number needed to treat = 7; 95% CI 3 –225).

Interpretation: Patients profited from the diagnosis of QoL deficits and tailored therapeutic options in their treatment of colorectal cancer. This trial confirmed the results of a previous RCT in breast cancer patients. The implementation of QoL concepts should become standard in treatment guidelines on cancer care.

Funding: Federal Ministry of Education and Research (BMBF; grant no. 01GY1339).

Clinical trial information: NCT02321813.

1. Research in context

1.1. Evidence before this study

This randomised trial built on preceding studies. In a literature review until Dec 1, 2013, we found robust evidence of the acceptability of the routine use of quality of life (QoL) measures to patients and physicians, consistent indications for improvements in patient–physician communication, but only two randomised trials could detect an improvement in patients' QoL. In a previous project, we have designed and implemented a complex intervention comprising systematic diagnosis and tailored treatment of QoL deficits during inpatient and outpatient care. Using this complex intervention, we were able to show the QoL improvement in a randomised trial of patients with breast cancer. It remains unclear if the intervention is also effective for routine use in patients with other cancer types or in other healthcare settings.

1.2. Added value of this study

Our results demonstrate that systematic QoL diagnosis and tailored QoL therapy in patients with primary colorectal cancer resulted in faster improvement of QoL during the first year after surgery in the context of guideline-conform treatment of colorectal cancer.

1.3. Implications of all the available evidence

The results of this trial investigating colorectal cancer patients are compatible with a previous randomised trial in breast cancer patients. Thus, the external validity of the intervention was established, a valuable finding in a scientific era characterised by discussions on the replication crisis in the life sciences. The implementation of QoL concepts in inpatient and outpatient care should become a standard feature in cancer treatment guidelines.

2. Introduction

There have been increasing efforts to develop interventions, which improve quality of life (QoL) for cancer patients in routine cancer care [1]. QoL interventions are highly acceptable to patients and physicians [2–5], improve patient–physician communication [3,6–8], and patients' QoL [6,9]. Interventions were conducted in single medical centre settings, such that outpatient care could not be considered in its full complexity, limiting the generalisability of results. For meeting the specific demands of cancer patients during both inpatient and outpatient medical care, a multiprofessional network encompassing all physicians (e.g., clinicians, oncologists, general practitioners) and other healthcare providers (e.g., psychotherapists, physiotherapists) supporting the patient during diagnosis, treatment and follow-up is needed. The Tumor Center Regensburg has designed and implemented a complex intervention comprising systematic diagnosis and tailored treatment of QoL deficits during inpatient and outpatient care [10–12]. The effectiveness of this intervention has been demonstrated in an RCT of patients with breast cancer, showing an improvement in women's QoL six months after surgery compared to patients with standard care [13]. It remains unclear if the intervention is also effective for routine use in patients with other cancer types or in other healthcare settings. Therefore, we adapted this intervention system to patients with colorectal cancer

that is the third most common cancer worldwide [14] (61,000 newly diagnosed patients/year in Germany), responsible for about 25,500 deaths per year in Germany [15]. These patients suffer considerably from QoL impairments [16,17] often related to postoperative complications [18], chemotherapy [19], or stoma [17]. Their specific demands differ in important aspects from those of breast cancer patients, due to invasive abdominal surgery, higher age, invalidity (stoma), gender distribution (both sexes affected to almost equally) and their aftercare, which is either provided by general practitioners or specialists in internal medicine.

The present RCT investigated the hypothesis that colorectal cancer patients who received systematic QoL diagnosis and tailored QoL therapy are better off in terms of their QoL 12 months after surgery than control patients who receive routine follow-up care.

3. Methods

3.1. Study design and participants

The study was designed as a two-arm randomised controlled prospective single-blind and pragmatic multicentre clinical trial of a complex intervention [13] that recruited consecutive patients from four participating German Cancer Society (DKG)-certified colorectal cancer centres in Bavaria, Germany (Krankenhaus Barmherzige Brüder, Department of Surgery, Regensburg; Caritas-Krankenhaus St. Josef, Department of Surgery, Regensburg; Klinikum Neumarkt, Department of Surgery, Neumarkt; Klinikum St. Elisabeth Straubing, Department of Surgery, Straubing). Inclusion criteria were (1) primary diagnosis of colorectal cancer; (2) surgical treatment in one of the four recruiting hospitals; and (3) informed consent. Exclusion criteria were the following: (1) unavailability of a study surgeon; (2) patient misclassified in the operation schedule (no primary operation, no colorectal tumour); (3) coordinating practitioner refused trial participation; (4) patient outside the defined study region; (5) age under 18 years; (6) pregnancy; (7) patient unable to fill out the QoL questionnaire (physical, psychological, cognitive, language reasons); (8) patient refused trial participation.

The trial was approved by the ethics committee of the University of Regensburg (reference number 12-101-0014). All participants provided written informed consent. The full study protocol was published before the completion of the trial [20].

3.2. Randomisation and masking

Randomisation and masking are described in detail in the study protocol [20]: Patients were randomly allocated to a QoL care pathway or to standard postoperative care. Balanced randomisation was generated with random permuted blocks of 20 patients followed by a sequence of 11 blocks with a second, simple randomisation using digit random number tables to create the allocation sequence. A blinded staff member at the Tumor Center Regensburg inserted 220 paper cards for group allocation in sealed opaque envelopes that were serially numbered and kept locked in a safe at the Tumor Center Regensburg. Only the two study coordinators (PLS, BS) had access. Clinicians in the four hospitals enrolled patients and sent the recruitment document to the Tumor Center Regensburg by fax. Once the recruitment document was received, the study coordinators opened the randomisation envelope with the highest consecutive number, and thus, assigned the patient either to the intervention or control group. Patients were masked to treatment allocation throughout the study (single-blind design), as well as clinicians. Coordinating practitioners (CP: general practitioner/oncologist who cares for the patient during aftercare) were informed about group allocation but obliged not to share their knowledge with the patient [20].

3.3. Procedures

3.3.1. Multiprofessional network for inpatient and outpatient care

In a preparatory phase, physicians in the hospitals and those acting as CP of pilot patients were familiarised with QoL assessment and administration of appropriate therapeutic options. The implementation strategy included QoL assessment in at least two pilot patients per hospital [21], as well as QoL-profile-based feedback on each patient's need for QoL-oriented care [12,20]. During the RCT, each CP was personally informed by the recruiting physician about the trial participation of his/her patient and individually trained in an educational outreach visit [20] by two study coordinators (PLS, BS). Intervention and control group patients were allowed to be treated by the same CP but were kept blind about group allocation. In addition, CPs received complete lists of QoL healthcare professionals practicing in the study region. A regional network structure for QoL healthcare providers had already been established during the earlier RCT in breast cancer patients [13] and was extended for the present RCT.

In total, 178 CPs treated patients in the RCT, and 17 clinicians in the four hospitals were responsible for patient recruitment. They were reimbursed for the aftercare through statuary health insurance. No additional study case-based payments were provided. The local network of healthcare providers encompassed 75 inpatient and outpatient therapists (n = 7 pain therapy; n = 13 psychotherapy; n = 10 social support; n = 15 nutritional counselling; n = 11 stoma care; n = 6 fitness; n = 10 physiotherapy; n = 3 support groups).

3.3.2. Patient-based assessments

Quality of life was measured with the European Organization for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30 (version 3.0) [22] and QLQ-CR29 [23,24]. EORTC QLQ-C30 addresses issues relevant to any cancer patient. Thirty items are aggregated into six functioning scales, three symptom scales and five single items. The EORTC QLQ-CR29 is specific for patients with colorectal cancer and consists of 29 items. Ten items are aggregated into four scales, and the remaining 19 items are interpreted on a single-item basis. For the present study, three single items, "flatulence," "faecal incontinence" and "embarrassment" were combined into one scale "discomfort during defecation." All scores were subjected to linear transformation and presented on scales ranging from 0 to 100 [25]. The linear transformation that was used in the present study in a uniform manner, with 0 denoting the negative (low functioning, high symptom burden) and 100 the positive end (high functioning, low symptom burden) of the continuum is in line with findings showing that patients and physicians prefer a uniform scoring of symptom and function domains [26]. A cutoff score of 50 points defined a need for QoL-therapy (<50 points) or no need for QoL therapy (≥ 50 points) [10,13]. This decision criterion was chosen because the present study aimed to highlight the patient's perspective of subjective impairment. This was operationalised by dichotomizing symptom scores with a majority of "quite a bit" and "very much" responses to "bad" side of the spectrum (<50) and "not at all" and "a little" responses to the "good" side (≥ 50) [27]. At the end of the trial, patients were checked for blindness with regard to the allocated study group.

3.3.3. Physician-based assessments

The following demographic and clinical patient variables were documented at study entry by recruiting clinicians: age, sex, marital status, number of children, American Society of Anesthesiologists (ASA) classification, tumour stage, date of surgery, surgical procedure, complications, comorbidities, (neo)adjuvant therapies, preoperative symptoms.

Patient's health status was repeatedly documented by CP during medical follow-up, including information about finished, current, and planned adjuvant therapies (chemotherapy, radiotherapy, antibody therapy), QoL therapies (pain therapy, psychotherapy, physiotherapy, social support, nutritional counselling, stoma care, fitness), and complications.

After the end of the trial, a *physician evaluation form,* including the following questions (answer: yes/no), was sent to all CPs: Do you find it useful to measure QoL during medical follow up of colorectal cancer patients? Was the workload caused by QoL measurements high?

3.3.4. Intervention and control

3.3.4.1. General procedure. Patients in both study arms completed a paper-and-pencil version of EORTC QLQ-C30 and QLQ-CR29. The first QoL measurement took place in the hospital at study entry 0–2 days before discharge (baseline). Further measurements were carried out during routine outpatient follow-up in the CP's practice. At the same timepoints (3, 6, 12, 18 months after surgery), CPs provided written information on their patients' health status. All data were sent to the Tumor Center Regensburg.

3.3.4.2. Intervention. Tailored QoL-therapies: The therapeutic options provided in our care network go beyond traditional psychooncological treatment and include the following options:

- psychotherapy
- social support
- nutritional counselling
- stoma care
- fitness
- physiotherapy
- pain therapy

For each therapeutic option, a network of professional therapists was established who met regularly in quality circles. The quality circles defined standards of care and provided continuing medical education. All professionals were certified in their respective fields (e.g., certified psychoonclogist or certified stoma nurse).

QoL-profile to indicate the need for a therapeutic intervention: After each QoL measurement in the intervention arm, the CP was sent a printout of the patient's QoL results in the form of a QoL-profile (Fig. 1). The QoL-profile showed a patient's QoL on 13 scales of QLQ-C30 and QLQ-CR29. These scales had been selected by a group of experts (physicians, psychologists) and discussed with patients, clinicians and therapists before starting the pilot phase of the trial. The selection was based on the results of the previous randomised trial in breast cancer patients [13], the appraisal of relevance for QoL of colorectal cancer patients, and the availability of specific therapies to improve QoL [20]. A cutoff score <50 points defined a need for QoL therapy [10,13,27]. Based on the patient and expert opinion obtained in the pilot phase, all 13 scales were relevant for colorectal cancer patients, and appropriate therapeutic options for treating specific QoL deficits were available.

If a need for QoL therapy was diagnosed within the QoL-profile (QoL<50 points), the CP received written recommendations for specific QoL therapies (Fig. 1). These were created by experts of the QoL unit at the Tumor Center Regensburg (physicians: MKS, BS; psychologist: PLS) who independently formulated their QoL recommendations. The QoL-profile, health status, and individual expert reports were discussed weekly at

consensus meetings of the three experts, resulting in an expert consensus report that was sent within one week to the CP of intervention group patients.

CPs received contact information of quality circle members to contact them for QoL therapy. Four weeks after each QoL measurement, a study coordinator contacted the CP by telephone to record whether anything had been done to improve the patient's QoL in response to the recommendations in the expert report. The clinical pathway is described more detailed in the study protocol [20].

3.3.4.3. Control. In the control arm, patients filled out QoL questionnaires at the same designated timepoints as in the intervention arm, but CPs received neither QoL-profiles nor recommendations for QoL therapy. However, QoL therapies could be ordered by CP ad hoc based on personal experience and guideline suggestions. Fig. 2 illustrates similarities and differences in both study arms.

3.4. Outcomes

The first primary endpoint (1) was the proportion of patients in the different groups with a need for QoL therapy 12 months postoperatively. A need for QoL therapy was defined as a score <50 points in at least one of 13 dimensions of the QoL-profile measured using EORTC QLQ-C30 and QLQ-CR29. The second primary endpoints (2) were the rates of patients with a need for QoL therapy in each of the 13 single dimensions of the QoL-profile 12 months after surgery. The primary endpoints were tested in the strict order (1), (2) [28]. Secondary endpoints were proportions of patients with a change in their need for QoL therapy from baseline (0 months) to primary endpoint (12 months).

3.5. Statistical analysis

The sample size was calculated according to the first primary endpoint. Based on our experience with the breast cancer RCT, we expected that 55% of the patients of the intervention group and 75% of the patients of the control group would indicate some need for QoL therapy at 12 months [13]. By setting α at 0·05 (two-sided) and power (1-β) at 0·80, 89 patients were needed per group to detect the hypothesized difference when calculating the chi-squared test. To compensate for 20% dropouts (death, refusal) within the 12-month observation period, we enrolled 110 patients per group [20].

All EORTC QLQ-C30 and QLQ-CR29 scales were aggregated according to the scoring instructions [25] and linearly transformed from 0 (lowest QoL, high symptom burden) to 100 (best QoL, no symptom burden).

Continuous variables are presented as mean (standard deviation), categorical variables as absolute and relative frequencies. The design for the two primary endpoints was based on a method of a fixed a priori ordered hypothesis [20]. Thus, the second primary endpoint will only be analysed if the null hypothesis of the first primary endpoint can be rejected ($p < 0{\cdot}05$). This design ensures a global alpha of 0·05. The analyses of the primary endpoints were conducted using the chi-squared test of independence. Absolute (ARR) and relative risk reductions (RRR) were calculated, as well as the number needed to treat (NNT). Confidence intervals (CI) for NNT were calculated using the Wald method.

Statistical tests regarding secondary endpoints used the $p < 0{\cdot}05$ significance threshold, but all results of the secondary endpoints were interpreted in an exploratory manner.

All analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). This trial was registered with ClinicalTrials.gov, number NCT02321813.

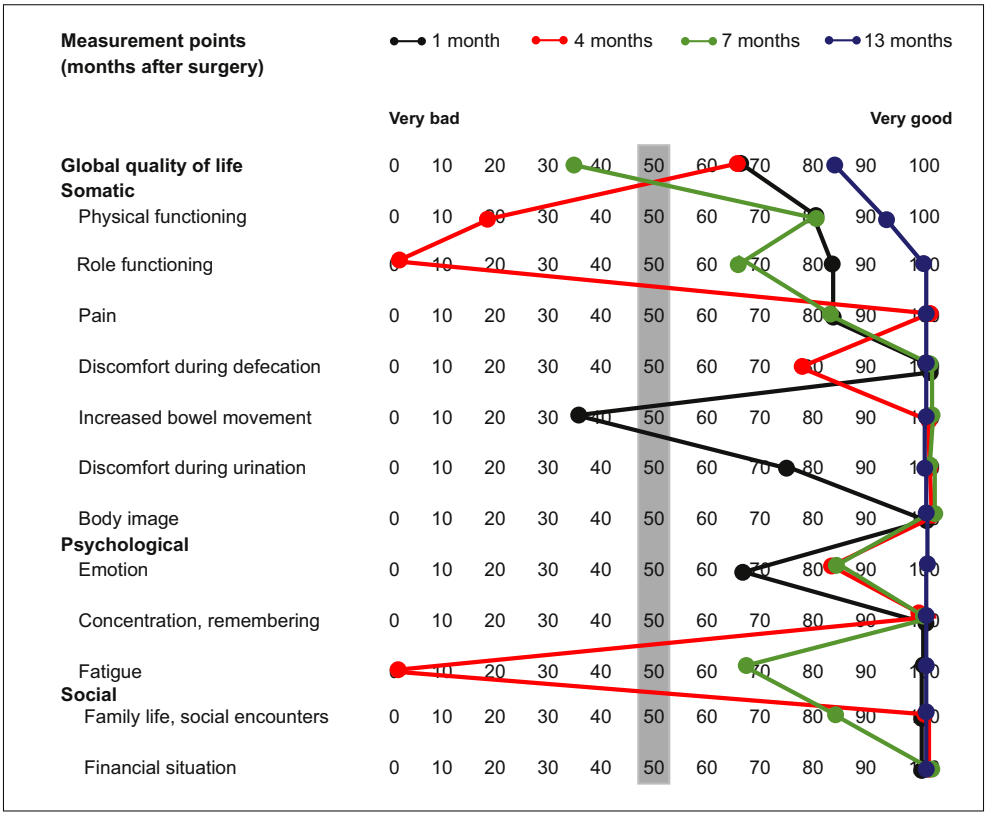
4. Results

Between Jan 13, 2014, and Oct 28, 2015, 552 patients were identified as potentially eligible. After the application of the above-stated study criteria, 271 patients were found to be ineligible and 61 declined to participate. The 220 remaining patients were randomly assigned to the intervention or control group (Fig. 3). The baseline characteristics of participants are shown in Table 1. Both groups were structurally equivalent (p-values are not reported due to biometric concerns [29]).

With respect to the first primary endpoint at 12 months [21], 35/83 (42%; 95% CI: 31–54%) of patients in the intervention group and 50/87 (57%; 95% CI: 46–68%) of patients in the control group had a need for QoL therapy in at least one dimension (χ^2 test, $p = 0{\cdot}046$). This corresponded to a 15% ARR (95% CI: 0–30), a 27% RRR (95% CI: 0–46), and an NNT of 7 (95% CI: 3–225; see Fig. 4).

A complementary analysis was performed to verify whether this result was also obtained when analysing the three items of the scale "discomfort during defecation" as single items (and not as one scale), as suggested by the EORTC [24]. The endpoint in this complementary analysis therefore encompassed 15 instead of 13 scales, and revealed that 41/82 (50%; 95% CI: 39–61%) of patients in the intervention group and 57/87 (66%; 95% CI: 55–75%) of patients in the control group had a need for QoL therapy in at least one dimension (χ^2 test, $p = 0{\cdot}041$; AAR = 16%, 95% CI: 0–30; RRR = 24%, 95% CI: 0–42; NNT = 6, 95% CI: 3–126). This confirmed our primary endpoint.

Fig. 4 shows that intervention and control groups differ with regard to their baseline need for QoL therapy at the disadvantage of the intervention group: 92/103 (89%; 95% CI: 82–95%) of intervention group patients and 86/104 (83%; 95% CI: 74–89%) of control patients



Expert report at discharge from hospital (1 month):

Findings: Increased bowel movement.
Interpretation: Good coping with the postoperative situation except for increased bowel movement.
Recommendation: In discussion with patient (shared decision-making) find out how he is coping with his stoma. Offer nutritional counseling to the patient if required. Recheck QoL in 3 months.

Expert report at 4th month after surgery:

Findings: Severe breakdowns in role functioning and fatigue, conspicuous loss in physical functioning.
Interpretation: Under adjuvant chemotherapy impaired coping due to reduced physical fitness and fatigue.
Recommendation: In communication with the patient try to clarify if the impairments still exist and either offer outpatient physiotherapy and fitness training or inpatient rehabilitation to the patient. Recheck QoL in 3 months.

Expert report at 7th month after surgery:

Findings: Except of global QoL all dimensions are in the healthy range.
Interpretation: Considerably improved QoL after fitness training and stoma reversal.
Recommendation: In discussion with patient find out why global QoL is impaired and recommend specific intervention by QoL therapist. Find attached a list with addresses of QoL therapists. Recheck QoL in 6 months.

Expert report at 13th month after surgery (primary endpoint):

Findings: All QoL dimensions are in the healthy range including global QoL.
Interpretation: Good coping with the situation under continued fitness training.
Recommendation: Recheck QoL in another 6 months.

Fig. 1. Quality of life (QoL) profile with recommendations for tailored QoL therapy in an intervention group patient (male with primary rectal carcinoma; 75 years, married, two children; prognostic classification ypT3 N2a M0 G1; laparoscopic low anterior resection with protective stoma, stoma reversal at 6 months; neoadjuvant radiotherapy and chemotherapy followed by adjuvant chemotherapy at 3 months). Grey bar = cutoff for a need for QoL therapy (<50 points).

were in need of QoL therapy at study entry (p = 0·170). In order to control for this difference, we conducted a subgroup analysis calculating differences between 12-month needs and baseline needs (Fig. 5). According to this analysis, 37/76 (49%; 95% CI: 37–60%) in the intervention group showed an improvement in their QoL, compared to only 22/85 (26%; 95% CI: 17–37%) in the control group (χ^2 test, p = 0·022). An analysis of

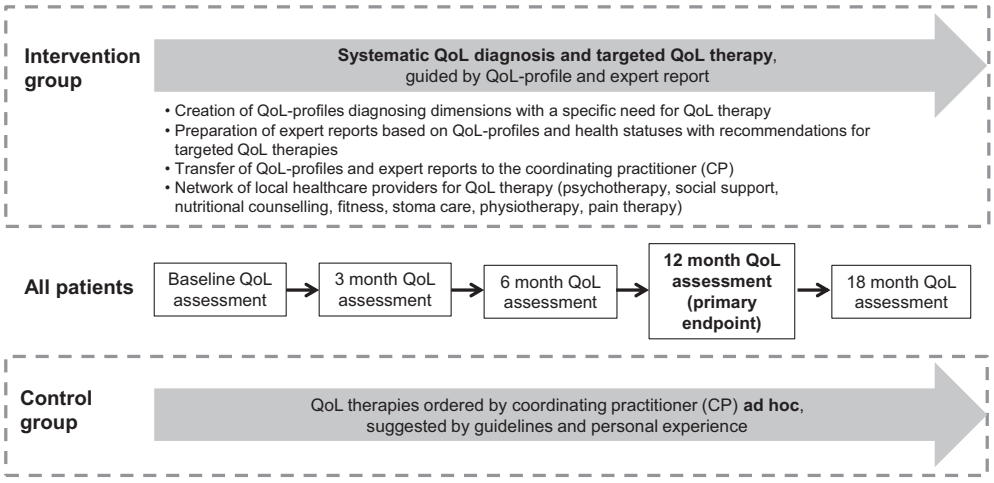


Fig. 2. Description of similarities and differences between the intervention and control arms. All patients received cancer-specific treatment, as suggested by locally tailored guidelines. All coordinating practitioners obtained the same quality of life (QoL) initiation (outreach visits, CME, opinion leaders).

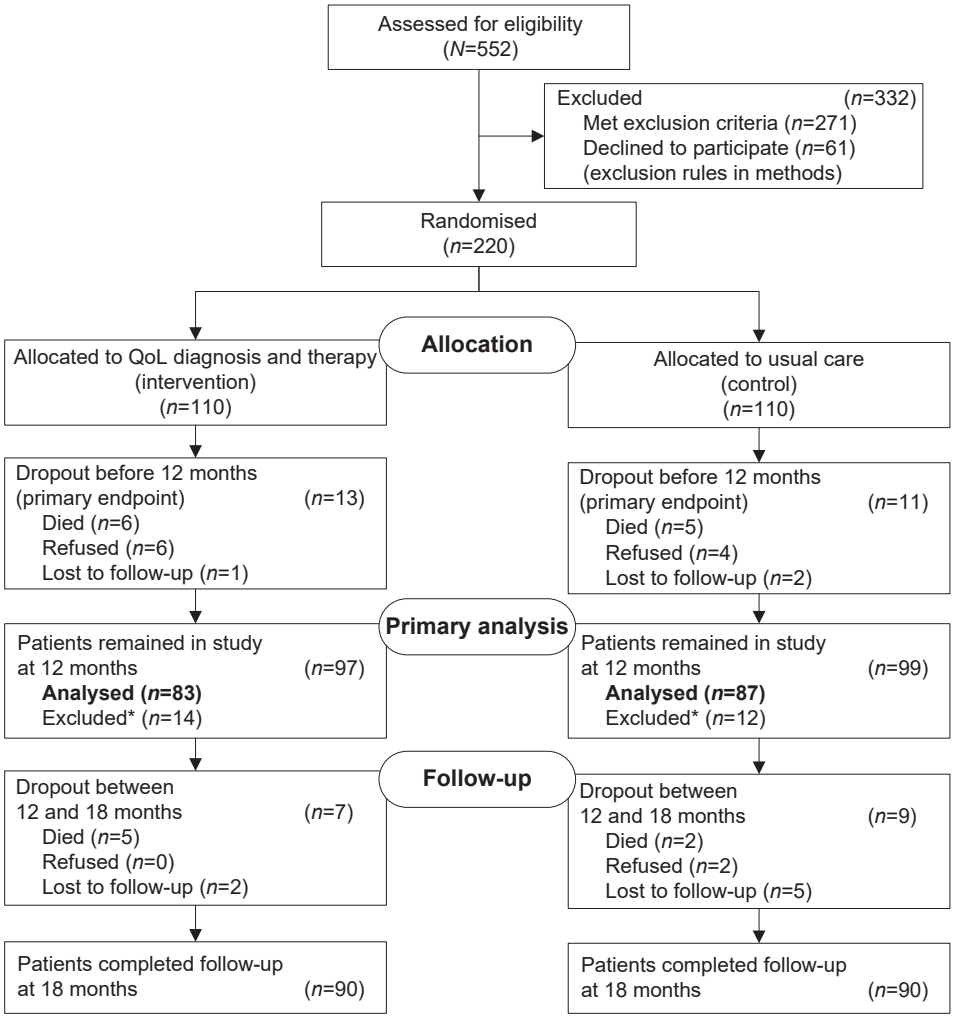


Fig. 3. CONSORT diagram. ∗Exclusion because of incomplete or missing quality of life (QoL) data at 12 months.

Table 1
Baseline characteristics of participants at study entry.

	No. (%) of participants	
	Intervention (QoL diagnosis and therapy; n = 110)	Control (routine care; n = 110)
Age, mean (SD), years	65·5 (11·8)	66·8 (10·1)
Male (%)	65 (60)	72 (66)
Marital status (%)		
Married	80 (73)	83 (75)
Unmarried	11 (10)	16 (15)
Widowed	11 (10)	5 (5)
Divorced	8 (7)	5 (5)
Unknown	0 (0)	1 (1)
Children (%)		
Yes	84 (76)	90 (82)
No	19 (17)	15 (14)
Unknown	7 (6)	5 (5)
Daily living[a] (%)		
Urban area	47 (43)	48 (44)
Rural area	63 (57)	62 (56)
Prognostic stage at diagnosis (%)		
UICC I	20 (18)	29 (26)
UICC II	30 (27)	27 (25)
UICC III	44 (40)	37 (34)
UICC IV	16 (15)	17 (15)
Primary site of disease (%)		
Colon	61 (55)	60 (55)
Rectum	49 (45)	47 (43)
Colon and rectum	0 (0)	3 (3)
Surgical access (%)		
Open	57 (52)	52 (47)
Laparoscopic	52 (47)	57 (52)
Endoscopic	0 (0)	1 (1)
Unknown	1 (1)	0 (0)
Type of resection (%)		
Right hemicolectomy	35 (32)	31 (28)
Left hemicolectomy	11 (10)	11 (10)
Sigmoid resection	6 (5)	12 (11)
Anterior resection	12 (11)	13 (12)
Low anterior resection	30 (27)	24 (22)
Abdominoperineal resection	9 (8)	11 (10)
Other	7 (6)	8 (7)
ASA[b] (%)		
ASA I	12 (11)	17 (15)
ASA II	43 (39)	45 (41)
ASA III	47 (43)	46 (42)
ASA IV	0 (0)	1 (1)
Unknown	8 (7)	1 (1)
Comorbidities (%)		
Cardiovascular	66 (60)	59 (54)
Kidney	12 (11)	8 (7)
Lung	14 (13)	11 (10)
Central nervous system	9 (8)	11 (10)
Stoma (%)	46 (42)	42 (38)
Reversed stoma	28 (61)	24 (57)
Preoperative symptoms (%)		
Abdominal pain	28 (25)	25 (23)
Anemia	19 (17)	16 (15)
Ileus	8 (7)	8 (7)
Bleeding	32 (29)	48 (44)
Days in hospital, mean (SD)	14·4 (9·9)	14·0 (8·3)
Neoadjuvant therapy (%)		
Chemotherapy + radiotherapy	29 (26)	24 (22)
Chemotherapy	1 (1)	1 (1)
Radiotherapy	4 (4)	1 (1)
No neoadjuvant therapy	76 (69)	84 (76)

(continued on next page)

Table 1 (*continued*)

[a] Urban: Regensburg city and county, rural: Neumarkt, Straubing, Straubing-Bogen, Kelheim, Schwandorf.
[b] American Society of Anesthesiologists.

the second primary endpoint comparing rates of patients with a need for QoL therapy at 12 months for the 13 single QoL dimensions revealed no significant differences between groups on any single scale (Table 2). Nevertheless, in 8/13 dimensions, the proportion of patients in need of QoL therapy was lower for intervention than for control group patients.

Rates of provided QoL therapies in the outpatient treatment over the course of 12 months are shown in the Supplementary Figure. There were no significant differences between both study arms.

A questionnaire asking for blindness after the end of the trial was filled out by 161 patients (intervention n = 78, control n = 83). 28% of the intervention group correctly believed to have been assigned to the intervention group, but also 32% of the control group incorrectly believed to be part of the intervention group. 15% of the control group patients thought to be included in the control group so did 13% of the intervention group patients. All other patients indicated that they had no idea about group allocation.

On average, each CP treated 1·26 patients (SD = 0·57; range 1–4) in the course of the study. 169 of the 178 participating CPs were mailed the physician evaluation form (reasons for exclusion: drop-out of patient before first contact with CP n = 4; retirement of CP n = 3; CP died n = 1; CP refused trial participation n = 1). Of those, 142/169 (84%) returned the evaluation questionnaire. The majority of CPs found the QoL assessment in the routine of colorectal cancer follow-up useful (121/136 [89%]), with an acceptable workload (122/138 [88%]).

5. Discussion

Systematic QoL diagnosis and tailored QoL therapy in patients with primary colorectal cancer resulted in faster improvement of QoL during the first year after surgery. This result confirms the earlier RCT in breast cancer patients [13]. The NNT of seven was the same in both trials, which may be taken as an indicator of a high external validity of the results. This replication in patients with a different tumour diagnosis who were treated in a different healthcare setting at another time is welcome in the current scientific debate on the replication crisis [30,31]. In contrast to most other trials

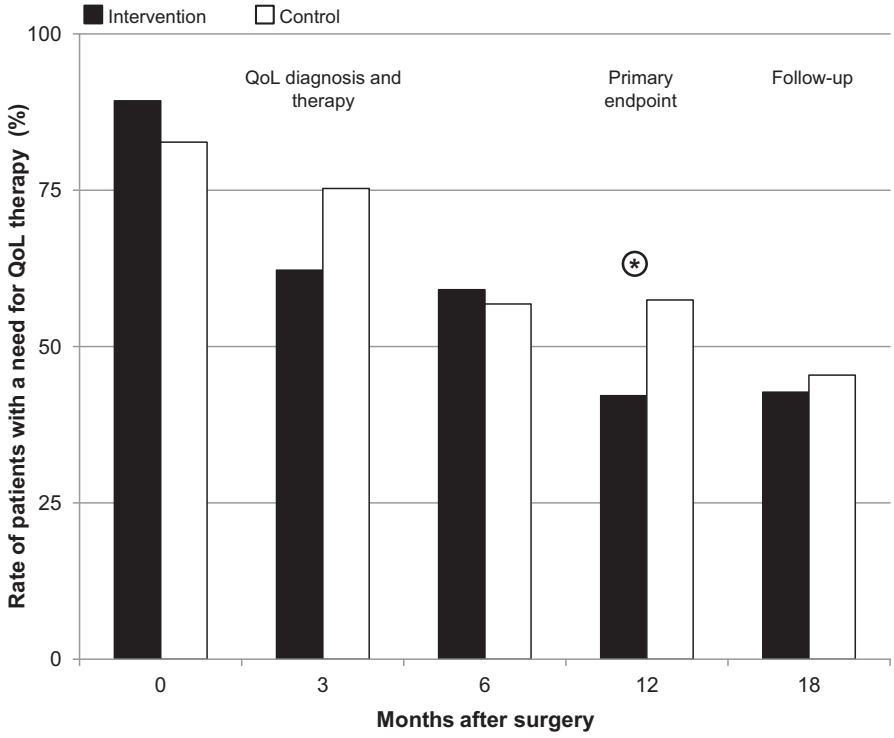


Fig. 4. Proportions of patients with a need for quality of life (QoL) therapy (QoL <50 points in at least 1 of 13 scales) following surgery: comparison of QoL deficit diagnosis and therapy (intervention) with routine postoperative care (control) over 18 months; χ^2 test: * $p < 0{\cdot}05$. 0 months: 92/103 versus 86/104, p = 0·170; 3 months: 61/98 versus 67/89, p = 0·055; 6 months: 52/88 versus 54/95, p = 0·758; 12 months: 35/83 versus 50/87, p = 0·046; 18 months: 38/89 versus 40/88, p = 0·712.

investigating the value of the routine use of patient-reported outcomes [1], our study revealed a significant improvement of QoL in the intervention arm. The most likely explanation for this effect is the fact that patients in the intervention group received a QoL-intervention that matched their actual needs, whereas patients in the control group received any of the available therapeutic options, regardless of what they indicated in the QoL assessment.

For capturing the idea of a multiprofessional therapeutic strategy caring for the diverse somatic, psychological and social needs of colorectal cancer patients during aftercare, a global primary endpoint was defined (need for QoL therapy in at least one of 13 dimensions) [20]. There was a nonsignificant trend for a better baseline QoL in the control group. When considering these different baseline scores in analysis, the effect of the intervention was even stronger. The second primary endpoint that compared rates of patients with a need for QoL therapy in each single QoL dimension did not reveal significant differences between the study arms. There was, however, a nonsignificant trend towards a lower proportion of patients with a need for QoL therapy in the intervention arm in 8 out of 13 QoL dimensions, which is in line with the first primary endpoint. It needs to be pointed out that the sample size calculation was based on the first global primary endpoint and not on the smaller subgroups of the second primary endpoint. There were fewer patients with a need for QoL therapy in every single dimension than patients with a global need for QoL therapy, such that the sample size was not large enough to detect small differences between the study arms.

Recommendations for tailored QoL therapies were created by a QoL unit instead of using an algorithm. This procedure was supposed to meet best the specific demands of our healthcare setting by incorporating a multiprofessional view and enhancing compliance of CPs. Other studies on QoL interventions could demonstrate a significant improvement of QoL without giving such concrete recommendations for QoL-oriented care [6,10]. It is an open question whether a simplified strategy (QoL-profile only in combination with the therapeutic network) would produce the same effect as the complex intervention as used in the present trial (QoL-profile plus recommendation plus therapeutic network). Clearly, a simplified strategy would enhance the sustainability of the QoL care system. Anyhow, a profound methodological and practical training of physicians using the QoL intervention remains an important requirement, as well as the availability of a therapeutic network.

The applied therapeutic spectrum is beyond symptom control [10] and includes various tailored QoL therapies, such as psychotherapy, social counselling, pain therapy, nutritional counselling, stoma care, fitness and

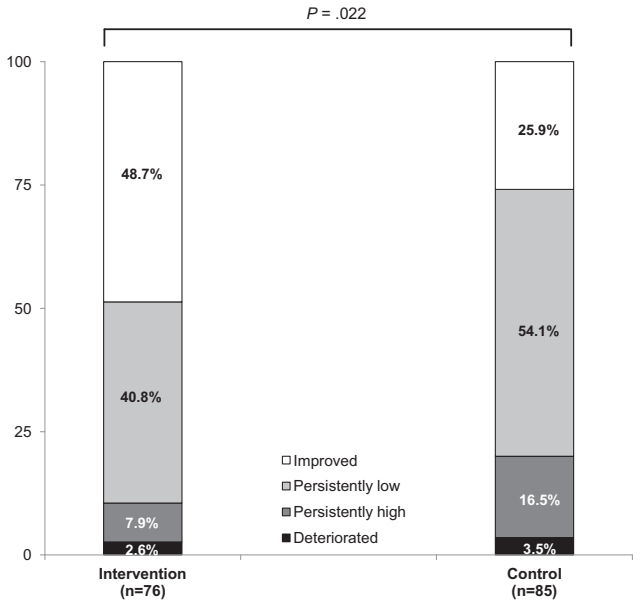


Fig. 5. Critical QoL values over time. Proportions of patients with a change in their need for quality of life (QoL) therapy from baseline (0 months) to primary endpoint (12 months) in the intervention and control groups: improved = QoL <50 points on at least 1 of 13 scales at 0 months and QoL ≥50 points on all 13 scales at 12 months; persistently high = QoL ≥50 points on all 13 scales at 0 and 12 months; persistently low = QoL <50 points on at least 1 of 13 scales at 0 and 12 months; deteriorated = QoL ≥50 points on all 13 scales at 0 months and QoL <50 points on at least 1 of 13 scales at 12 months. *P*-value was calculated using χ^2 test comparing study arms based on the four categories of comparison (improved, persistently low, persistently high, deteriorated).

Table 2
First and second primary endpoints: proportions of patients with a need for quality of life (QoL)-oriented therapy (<50 points) in at least 1 of 13 QoL dimensions (first primary endpoint) and in 13 single QoL dimensions (second primary endpoint) at 12 months.

QoL dimension (second primary endpoint)	Intervention (QoL diagnosis and therapy; n = 83)	Control (routine care; n = 87)	*p*-value[a]
Global QoL	20%	14%	0·246
Physical functioning	10%	3%	0·101
Role functioning	18%	20%	0·807
Pain	12%	11%	0·911
Discomfort during defecation	7%	14%	0·173
Stool frequency	8%	13%	0·373
Urinary incontinence	19%	21%	0·818
Body image	5%	8%	0·393
Emotional functioning	13%	15%	0·752
Cognitive functioning	6%	8%	0·607
Fatigue	19%	21%	0·818
Social functioning	10%	10%	0·878
Financial impact	11%	6%	0·227
Total (first primary endpoint)[b]	42%	57%	0·046*

[a] All *p*-values are derived from χ2 tests, *$p < 0·05$.
[b] Need for QoL therapy (QoL <50 points) in at least 1 of 13 QoL dimensions.

physiotherapy. These therapies were embedded in a network of regional healthcare professionals. Generally, therapeutic approaches that strive to improve patients' QoL must be evaluated in the context of the overall healthcare system covering patients within a given region. In Germany, medical aftercare for cancer patients is regulated by national practice guidelines, but there are still no comparable standards for QoL-related issues. For closing this care gap, our intervention was based on an integrated treatment embedded in the inpatient and outpatient setting and comprised a large number of medical and nonmedical specialists. These professionals participated in quality circles and covered a circumscribed geographical region.

The low dropout rates and high follow-up rates of 90/110 (82%) in both study arms, as well as the low CP dropout rate during the study of 1/178 (1%), indicate good acceptance and feasibility of the intervention. The majority of CPs evaluated the intervention as helpful and wished to receive QoL-profiles for other patients as well.

There are some limitations that need to be considered when interpreting the study results. For each study patient (intervention and control arm) we recorded the administration of QoL therapy in a binary fashion (yes/no), without further specifying the duration or intensity of this therapy. However, in order to provide a comparably high quality of care standards, CPs were required to select healthcare providers that were listed within the regional therapeutic network. Furthermore, the RCT is limited to a circumscribed region in Germany, which made it possible to establish local network structures. Although this network played a central role in the study, we also recognise that in remote regions, specific QoL therapies were often less available. Therefore, the intervention should be reevaluated for other regions and healthcare systems. In addition, it is important to improve healthcare structures in rural areas. Overall, colorectal cancer patients who received medical treatment according to current practice guidelines profited from additional QoL diagnosis and tailored therapeutic options. This trial confirmed the results of a previous RCT in breast cancer patients. The implementation of QoL concepts in inpatient and outpatient care should become a standard feature in cancer treatment guidelines.

Contributors

MKS was the principal investigator of the trial. All authors contributed to the conception and design of the study. FZ did the sample size calculations. BS, AF, JG, RO, PP, and PLS were involved in the collection and assembly of the data. MK, FZ and PLS were responsible for data analysis. All authors contributed to the interpretation of the data, the preparation and writing of the manuscript, and approved the final manuscript.

Role of funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility.

Conflict of interest statement

We declare no competing interests.

Acknowledgments

The study was funded by the Federal Ministry of Education and Research (BMBF) (grant no. 01GY1339). The authors would like to thank the study participants, the four recruiting colorectal cancer centres, and the many coordinating practitioners and healthcare professionals. We are grateful to the late Prof. Wilfried Lorenz († 2014) for his expertise in the development of the study conception and design. We also acknowledge the contributions of the late Dr. Brigitte Ernst († 2019) to the evolution of the Tumor Center Regensburg and to patient-centred oncological care.

Appendix

Regensburg QoL Study Group, Germany: Annegret Altendorfer, Christina Apel, Dr. Vladimir Arcybasov, Markus Artner, Dr. Olga Arzberger, Dr. Erwin Bambl, Dr. Martin Bauer, Dr. Irmengard Begemann, Dr. Norbert Bloos, Dr. Maximilian Bock, Dr. Brigitte Böhmer, Dr. Clemens Bonke, Dr. Christine Böttger, Dr. Bruno Brandscherdt, Dr. Michael Braun, Dr. Wolfgang Bräutigam, Dr. Marion Brunner, Dr. Monika Brunner, Dr. Thomas Bucher, Dr. Norbert Buchmeier, Dr. Daniel Bulling, Dr. Daniela Cameron, Dr. Viktor Damjantschitsch, Dr, Matthias Demandt, Dr. Carlos Diaz, Dr. Heinrich Dickert, Elvira Dommel, Dr. Franz Ehrnsperger, Dr. Diethard Eibl, Dr. Peter Eibl, Dr. Verena Engelbrecht, Dr. Axel Enhuber, Dr. Michaela Faltermeier, Georg Feldmer, Dr. Joachim Feldner, Dr. Hans Peter Ferstl, Dr. Robert Franz, Dr. Richard Franzke, Prof. Stephan Fritz, Dr. Thomas Fuchs, Dr. Hans-Jürgen Füßl, Dr. Siegfried Gehrmann, Dr. Michael Geisler, Micheline Geldsetzer, Karin Germann-Bauer, Dr. Vera-Maria Gohlke, Bernd Graf, Wolfgang Grampp, Dr. Erich Gruber, Bernhard Grumbeck, Dr. Christopher Haberl, Dr. Hans-Jürgen Hackl, Dr. Jürgen Hamberger, Dr. Rupert Hanrieder, Dr. Thomas Harloff, Dr. Werner Hartl, Dr. Matthias Hartmann, Dr. Hans Georg Haser, Mark Hauer, Dr. Ralf Hauer, Dr. Gerold Haug, Dr. Christiane Heidrich, Dr. Jessica Hentschel, Dr. Morgens Heusinger, Dr. Wolfgang Hiergeist, Thomas Hinrichs, Dr. Sonja Hofmann, Dr. Hans-Joachim Horn, Elena Huber, Dr. Ulrich Ihle, Dr. Thomas Irmer, Dr. Johannes Jockel, Dr. Josef Käss, Dr. Manfred Kästel, Ralf Kecke, Dr. Hans Kehrer, Dr. Elvira Keller, Dr. Gerd Kelly, Dr. Thomas Kestler, Dr. Bernhard Kiefmann, Dr. Josef Kindler, Dr. Elke Kistner, Dr. Peter Klein, Hubert Kleindienst, Dr. Marius Kleisch-Nicoara, Dr. Horst Kneiβl, Dr. Stefan Kobras, Dr. Jens Kohlmeyer, Dr. Wolfgang Kraus, Dr. Katrin Krauss, Dr. Klaus Kubitschek, Dr. Lisa Kuchler, Alois Kuhn, Dr. Ulrike Kuhrt, Dr. Andrea Kulig, Magda van de Laar, Dr. Benedikt Lampl, Dr. Thomas Langer, Sonja Leeb, Dr. Karl Lehmeyer, Dr. Friedrich Lehner, Dr. Thomas Leibig, Dr. Gudrun Liebig-Hörl, Gunter Lingner, Dr. Petra Lütz, Dr. Frederik Mader, Dr. Judith Maier, Dr. Anita Malterer, Dr. Franz Mandlinger, Dr. Rudolf Männer, Dr. Ralf Marx, Dr. Christine Meier, Dr. Michael Meinhardt, Dr. Barbara Meyer, Dr. Susanne Meyer, Dr. Klaus Michels, Dr. Franz Mohr, Dr. Roland Muggendorfer, Dr. Birgit Mühlenbruch, Dr. Andreas Müller, Dr. Helmut Müller, Dr. Egid Mürbeth, Dr. Maria Neef, Dr. Klaus Neumann, Dr. Heike Nöller, Dr. Johann Nusser, Martin Ochsenkühn, Daniela Pacini, Dr. Robert Pavlik, Dr. Veronika Peller, Dr. Birgit Pelz-Knöbl, Dr. Peter Perzl, Renate Peschke, Dr. Anton Peter, Dr. Martin Pfefferkorn, Dr. Rafael Piazolo, Dr. Andreas Piberger, Dr. Andrea Plank, Dr. Angelika Plank-Wihr, Dr. Herbert Platzer, Dr. Anca-Elena Pletl, Dr. Georg Preininger, Dr. Christoph Puchner, Maria Putz, Dr. Konstantin Radi, Bruno Ratter, Dr. Uwe Rauprich, Dr. Carl Rauscher, Dr. Jürgen Reichold, Dr. Birgit Richter, Dr. Adolf Ried, Dr. Heiko Rieder, Dr. Roland Rischbeck, Dr. Michael Riβmann, Dr. Ulrike Röschl, Dr. Godehard Rutz, Dr. Florian Santner, Prof. Claus Schäfer, Dr. Sandra Scheffczyk, Erwin Schierl, Dr. Gernot Schindler, Dr. Anke Schlenska-Lange, Dr. Anna Schneider, Dr. Vera Schnell, Dr. Manfred Schöberl, Dr. Bernhard Schönhärl, Kristina Schreiber, Dr. Barbara Schutt, Petra Schwedmann, Dr. Elisabeth Schweitzer, Dr. Georg Schwindl, Dr. Georg Sedlmayer, Dr. Gerhard Seiler, Dr. Axel Selchert, Dr. Stefan Semmler, Dr. Thomas Seubert, Dr. Erich Simon, Dr. Wolfgang Sinzker, Dr. Gabriele Sostmeier († 2015), Dr. Jens Spaltmann, Dr. Christian Spieβl, Dr. Reinhard Spreyer, Michael Staab, Dr. Simone Steinbild, Dr. Catarina Stosiek, Dr. Elisabeth Sturm-Wittl, Dr. Angela Tautrim, Dr. Anton Tkaczyk, Dr. Tümmler Fred, Dr. Hans Tylla, Dr. Jan Hendrik van de Berg, Dr. Marie-Luise Vogel, Dr. Peter Voigtländer, Dr. Gerhard Wagner, Dr. Hubert Wagner, Dr. Richard Wagner, Dr. Anita Walter, Franz Walter, Dr. Irene Walter, Dr. Robert Weber, Dr. Sandra Wegscheid, Dr. Julia Weigand, Thomas Weisbarth, Dr. Raphael Weiβgerber, Dr. Bernd Wellhöfer, Dr. Wido Wilke, Dr. Ina Winter, Dr. Karl Witzmann, Dr. Franz Wolf, Dr. Johannes Wolf, Christine Wöll-Kobler, Dr. Andrea Wonka, Renate Woschée, Dr. Verena Zahn, Dr. Elke Zankel, Dr. Tanja Zilch, Dr. Ruth Zimmermann, Dr. Marc Zörerbauer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2020.01.025.

References

[1] Kotronoulas G, Kearney N, Maguire R, Harrow A, Domenica DD, Croy S, et al. What is the value of the routine use of patient-reported outcome measures toward improvement of patient outcomes, processes of care, and health service outcomes in cancer care? A systematic review of controlled trials. J Clin Oncol 2014;32:1480–501.

[2] Detmar SB, Aaronson NK, Wever LDV, Muller M, Schornagel JH. How are you feeling? Who wants to know? Patients' and oncologists' preferences for discussing health-related quality-of-life issues. J Clin Oncol 2000;18:3295–301.

[3] Detmar S, Muller M, Schornagel J, Wever LDV, Aaronson NK. Health-related quality-of-life assessments and patient-physician communication. A randomized controlled trial. J Am Med Assoc 2002;288:3027–34.

[4] Braeken APBM, Kempen GIJM, Eekers D, van Gils FCJM, Houben RMA, Lechner L. The usefulness and feasibility of a screening instrument to identify psychosocial problems in patients receiving curative radiotherapy: a process evaluation. BMC Canc 2011;11:479.

[5] Cleeland CS, Wang XS, Shi Q, Mendoza TR, Wright SL, Berry MD, et al. Automated symptom alerts reduce postoperative symptom severity after cancer surgery: a randomized controlled clinical trial. J Clin Oncol 2011;29:994–1000.

[6] Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring quality of life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol 2004;22:714–24.

[7] Berry DL, Blumenstein BA, Halpenny B, Wolpin S, Fann JR, Austin-Seymour M, et al. Enhancing patient-provider communication with the electronic self-report assessment for cancer: a randomized trial. J Clin Oncol 2011;29:1029–35.

[8] Takeuchi EE, Keding A, Awad N, Hofmann U, Campbell LJ, Selby PJ, et al. Impact of patient-reported outcomes in oncology: a longitudinal analysis of patient-physician communication. J Clin Oncol 2011;29:2910–7.

[9] Basch E, Deal AM, Kris MG, Scher HI, Hudis CA, Sabbatini P, et al. Symptom monitoring with patient-reported outcomes during routine cancer treatment: a randomized controlled trial. J Clin Oncol 2016;34:557–65.

[10] Klinkhammer-Schalke M, Koller M, Wyatt JC, Steinger B, Ehret C, Ernst B, et al. Quality of life diagnosis and therapy as complex intervention for improvement of health in breast cancer patients: delineating the conceptual, methodological, and logistic requirements (modeling). Langenbeck's Arch Surg 2008;393:1–12.

[11] Klinkhammer-Schalke M, Koller M, Ehret C, Steinger B, Ernst B, Wyatt JC, et al. Implementing a system of quality of life diagnosis and therapy for breast cancer patients: results of an exploratory trial as prerequisite for a subsequent RCT. Br J Canc 2008;99:415–22.

[12] Campbell M, Fitzpatrick R, Haines A, Sandercock P, Tyrer P. Framework for design and evaluation of complex interventions to improve health. BMJ 2000;321:694–6.

[13] Klinkhammer-Schalke M, Koller M, Steinger B, Ehret C, Ernst B, Wyatt JC, et al. Direct improvement of quality of life using a tailored quality of life diagnosis and therapy approach: randomized trial in 200 women with breast cancer. Br J Canc 2012;106:826–38.

[14] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jema A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[15] Robert Koch-Institut und die Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Krebs in Deutschland 2013/2014. 11th ed. Berlin: Robert Koch-Institut; 2017.

[16] Quach C, Sanoff HK, Williams GR, Lyons JC, Reeve BB. Impact of colorectal cancer diagnosis and treatment on health-related quality of life among older Americans: a population-based, case-control study. Cancer 2015;121:943–50.

[17] Downing A, Morris EJA, Richards M, Corner J, Wright P, Sebag-Montefiore D, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. J Clin Oncol 2015;33:616–24.

[18] Di Cristofaro L, Ruffolo C, Pinto E, Massa M, Antoniutti M, Cagol M, et al. Complications after surgery for colorectal cancer affect quality of life and surgeon-patient relationship. Colorectal Dis 2014;16:O407–19.

[19] Pettersson G, Berterö C, Unosson M, Börjeson S. Symptom prevalence, frequency, severity, and distress during chemotherapy for patients with colorectal cancer. Support Care Canc 2014;22:1171–9.

[20] Klinkhammer-Schalke M, Lindberg P, Koller M, Wyatt JC, Hofstädter F, Lorenz W, et al. Direct improvement of quality of life in colorectal cancer patients using a tailored pathway with quality of life diagnosis and therapy (DIQOL): study protocol for a randomised controlled trial. Trials 2015;16:460.

[21] Lindberg P, Steinger B, Lorenz W, Koller M, Klinkhammer-Schalke M. Lebensqualitätsdiagnostik und -therapie bei Patienten mit primärem kolorektalem Karzinom im Rahmen einer komplexen Intervention: ergebnisse aus der Pilotphase. Palliativmedizin 2014;15(suppl; abstr V142):41.

[22] Aaronson NK, Ahmdezai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

[23] Gujral S, Conroy T, Fleissner C, Sezer O, King PM, Avery KNL, et al. Assessing quality of life in patients with colorectal cancer: an update of the EORTC quality of life questionnaire. Eur J Canc 2007;43:1564–73.

[24] Whistance RN, Conroy T, Chie W, Costantini A, Sezer O, Koller M, et al. Clinical and psychometric validation of the EORTC QLQ-CR29 questionnaire module to assess health-related quality of life in patients with colorectal cancer. Eur J Canc 2009;45:3017–26.

[25] Fayers P, Aaronson N, Bjordal K, Curran D, Groenvold M. EORTC QLQ-C30 scoring manual. 9th ed. Brussels: EORTC Study Group on Quality of Life; 2001.

[26] Snyder CF, Smith K, Bantug E, Tolbert EE, Blackford AL, Brundage MD. What do these scores mean? Presenting patient-reported outcomes data to patients and clinicians to improve interpretability. Cancer 2017;123:1848–59.

[27] Koller M, Lorenz W. Quality of life: a deconstruction for clinicians. J R Soc Med 2002;95:481–8.

[28] Wiens B. A fixed sequence Bonferroni procedure for testing multiple endpoints. Pharmaceut Stat 2003;2:211–5.

[29] CONSORT. http://www.consort-statement.org/checklists/view/32–consort-2010/510-baseline-data. [Accessed 8 January 2020].

[30] Nosek BA, Aarts AA, Anderson CJ, Kappes HB. Estimating the reproducibility of psychological science. Science 2015;349.aac4716–aac4716.

[31] Ioannidis JPA, Greenland S, Hlatky MA, Khoury MJ, Macleod MR, Moher D, et al. Increasing value and reducing waste in research design, conduct, and analysis. Lancet 2014;383:166–75.