

Quality of life across chemotherapy lines in patients with advanced colorectal cancer: a prospective single-center observational study

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Abstract

Background Palliative chemotherapy in patients with nonresectable advanced colorectal carcinoma is performed to prolong survival, alleviate tumor-associated symptoms, and maintain or improve health-related quality of life (HRQOL). In this prospective single-center observational study, we assessed HRQOL across the various lines of palliative chemotherapy.

Methods HRQOL data were acquired using the EORTC Quality of Life Questionnaire-C30 (QLQ-C30) questionnaire. The first assessment was performed at the beginning of each chemotherapy line, the second after three cycles, and the third at the end of chemotherapy. Further assessments were conducted during checkups every 3 months in our outpatient unit.

Results In total, 100 consecutive patients with colorectal carcinoma (mean age 66.4 years; 60 % men) treated with palliative chemotherapy were recruited. Generally, QOL deteriorated constantly across time. Physical functioning, fatigue, pain, dyspnea, and appetite worsened steadily from first-line chemotherapy to the later treatment phase. Global QOL, emotional functioning, and role functioning improved slightly after the end of first-line chemotherapy, deteriorated during second-line chemotherapy to the level of first-line chemotherapy, and further deteriorated in the later treatment phases. In additional analyses, we found the largest differences between patients with and without a treatment response for pain (19.0 vs. 37.2 points) and appetite loss (17.4 vs. 32.7 points).

Conclusion The individual QOL domains deteriorated constantly across time. Our data indicate that patients undergoing first- and second-line palliative chemotherapy experience stabilization of global QOL and psychosocial symptoms. We also found that unselected patients who achieved a treatment response had a lower symptom burden and better QOL than did patients with progressive disease.

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Keywords Advanced colorectal cancer · Quality of life · Palliative chemotherapy · Electronic patient-reported outcome monitoring

Background

Colorectal cancer (CRC) is the third most common cause of cancer death in both men and women in Europe and the USA. The aims of chemotherapy in patients with nonresectable advanced CRC are to prolong survival, control symptoms, and maintain or improve quality of life (QOL) [1].

The median overall survival for patients with unresectable advanced CRC who receive best supportive care alone is

approximately 5 to 6 months. Systemic chemotherapy produces meaningful improvements in median survival and progression-free survival [2].

For many decades, 5-fluorouracil was the main active agent in the treatment of CRC, providing a median survival of about 1 year [3]. This has changed markedly since the year 2000. With the approval of irinotecan and oxaliplatin in combination with 5-fluorouracil, the median overall survival has increased to 19 months [4, 5]. The number of therapeutic options for CRC further increased with the addition of several humanized monoclonal antibodies to vascular endothelial growth factor and epidermal growth factor, and the median survival for patients with metastatic disease is now approximately 24 months [6–8].

In addition to delaying disease progression, maintenance of health-related QOL (HRQOL) is a particularly important aim of treatment in patients with metastatic disease [1]. HRQOL can be formally defined as “the extent to which one’s usual or expected physical, emotional, and social well-being are affected by a medical condition and its treatment” [9]. This definition incorporates the two widely accepted aspects of QOL: subjectivity and multidimensionality [10].

In previous randomized trials, HRQOL measurement was performed at baseline and at determined intervals during administration of a specific palliative chemotherapy line [11, 12]. Knowledge of the longitudinal course of QOL across different chemotherapy lines is almost completely lacking. Thus, the objective of our study was to analyze and compare patient-reported HRQOL measured by repeated computer-assisted completion of validated questionnaires in patients with nonresectable advanced CRC while they underwent treatment with several palliative chemotherapy lines.

Patients and methods

Sample

Patients were consecutively included in the study upon starting a palliative chemotherapy line according to standard guidelines [1, 13]. The inclusion criteria were a diagnosis of metastatic CRC, starting palliative chemotherapy, no overt cognitive impairment, age of >18 years, and written informed consent. The first assessment was performed at the beginning of chemotherapy, the second after three cycles, and the third at the end of chemotherapy (after six cycles). Response was assessed using interval radiographic evaluation (every 3 months). Radiographic tumor response was quantified using Response Evaluation Criteria in Solid Tumors (RECIST) [14]. Further interviews were conducted during checkups every 3 months in our clinic and when another chemotherapy line was started for treatment of progressive disease. QOL

assessments continued until the patient died or was unable to complete the questionnaire or at a maximum of 3 years after inclusion in the study.

QOL data collection

QOL was assessed with the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (QLQ-C30), an internationally validated and widely used cancer-specific QOL questionnaire [15]. This questionnaire is the most frequently used instrument for assessment of HRQOL in patients with CRC. It comprises five functioning scales (physical, role, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, and nausea and vomiting), a global QOL scale, and six single items that assess additional problems commonly reported by patients with cancer (dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial difficulties). We administered only the QLQ-C30 and not the additional CRC module, the QLQ-CR29, to limit patient burden introduced by questionnaire length and repeated assessments.

Differences in QOL scores of >20, 10 to 20, and 5 to 10 points were considered large, moderate, and small, respectively [16]. To facilitate both data collection and analysis, QOL data capture was performed electronically using tablet PCs running Computer-based Health Evaluation System software [17]. A study nurse gave these tablet PCs to patients and asked them to complete the QLQ-C30. The study nurse provided further information and assistance to patients with questions or concerns. Assessments took place in the patients’ rooms during their inpatient or day clinic stay for computed tomography evaluation.

Clinical and sociodemographic data were collected from the hospital records and entered in the Computer-based Health Evaluation System database to match patient-reported outcome data. This study was approved by the ethics committee of the state medical board of Upper Austria.

Statistical analysis

Analysis of differences in QOL among different chemotherapy lines was performed with linear mixed models. The models comprised the chemotherapy line as the fixed effect and the QOL scores as dependent variables. All chemotherapy lines beyond the second line were collapsed to a category labeled “third+ line.” The variables were divided into separate categories for the period of chemotherapy administration and the period during which patients received no active anticancer treatment (intervals between chemotherapy administrations). Additionally, the model employed a first-order autoregressive covariance structure and a random intercept at the patient

level. We conducted an additional analysis of the association between QOL and response to treatment. Because the chemotherapy line was strongly associated with treatment response, we did not include both variables in the same model; instead, we performed another analysis using the same model described above, but with treatment response instead of chemotherapy as the fixed effect.

Results

Patient characteristics

In total, 100 consecutive patients with nonresectable advanced CRC were recruited at the Department of Internal Medicine, Hospital Wels-Grieskirchen, Austria from February 2007 to September 2011 and assessed for a maximum of 3 years. Sixty percent of the patients were men, and the mean patient age was 66.4 years (standard deviation 10.6). At the time of recruitment, 73 patients were starting first-line palliative chemotherapy and 27 patients were at the start of the second-line chemotherapy. Further details are provided in Table 1.

Twenty-five percent of the patients died during the first year after study inclusion, 29 % died during the second year, and 26 % died during the third year. The median survival time after study inclusion was 21.8 months (95 % confidence interval 15.6–28.0).

The questionnaire completion rates ranged from 65 to 100 % for assessment time points during the first year after study inclusion. For time points during the second year, the completion rate was between 61 and 70 %, and during the third year, between 45 and 71 %. These percentages refer to the total number of patients alive in that period.

Comparison of QOL across chemotherapy lines

The main focus of our analysis was determination of the trajectories of the individual QOL domains covered by the QLQ-C30 across the various lines of palliative chemotherapy. In general, QOL deteriorated constantly across time. Constipation, financial impact, and taste alterations were the only domains that did not significantly change over time.

Physical functioning, fatigue, pain, dyspnea, and appetite loss worsened more or less steadily from first-line chemotherapy to the later treatment phases; however, physical functioning was similar in the off-treatment period following first-line chemotherapy (70.5 points) and second-line chemotherapy (71.1 points). Additionally, fatigue and pain had nearly the same levels during and after first-line chemotherapy.

Global QOL, emotional functioning, and role functioning improved by about 5 points after the end of first-line chemotherapy, deteriorated during second-line chemotherapy to the level of first-line chemotherapy, and further deteriorated in the

Table 1 Patient characteristics ($n = 100$)

Age	Mean (SD)	66.4 (10.6)
	Range	37–85
Sex, n (%)	Men	60 (60.0)
	Women	40 (40.0)
Chemotherapy line (n)	First-line palliative	73
	Post first-line (off-treatment)	38
	Second-line palliative	63
	Post second-line (off-treatment)	27
	Third-line or more palliative	47
	Post third-line (off-treatment)	22
Chemotherapy regimen (%) ^a	First-line palliative	
	FU/FA/oxaliplatin	16.7
	FU/leucovorin	15.3
	FU/FA/irinotecan/panitumumab	15.3
	FU/FA/oxaliplatin/bevacizumab	12.5
	Second-line palliative	
	FU/FA/irinotecan	18.3
	Panitumumab	15.0
	FU/FA/irinotecan/cetuximab	11.7
	FU/FA/oxaliplatin/bevacizumab	10.0
	Third-line or more palliative	
	Panitumumab	17.6
	FU/FA/bevacizumab	17.6
FU/FA/oxaliplatin	12.2	
FU/FA/oxaliplatin/bevacizumab	9.5	

^a Percentages are based on the number of the patients in the respective chemotherapy line

later treatment phases. Role functioning deteriorated from 56.7 to 47.8 points immediately after second-line chemotherapy, whereas global QOL and emotional functioning did not decrease until third-line chemotherapy.

Social functioning was similar during and after first-line chemotherapy at 74.8 and 75.1 points, respectively; it stabilized at 64.9 to 68.6 points between second-line chemotherapy and later chemotherapy lines, and showed the most severe impairment at 57.9 points during the off-treatment phases of the third+ chemotherapy lines.

Sleep disturbances remained rather stable at 26.9 to 30.0 points during and after the first two chemotherapy lines and worsened to 35.4 to 44.2 points during and after the third+ chemotherapy lines.

Diarrhea was generally worse during treatment and less severe in the periods between two chemotherapy lines. The average diarrhea score was 29.2 points during third+ chemotherapy; this substantially exceeded the scores during first-line (21.7 points) and second-line (18.8 points) chemotherapy. Further details are shown in Tables 2 and 3 and Figs. 1 and 2.

In a further analysis, we investigated the impact of response to treatment according to RECIST (progressive disease vs.

Table 2 EORTC QLQ-C30 functioning trajectories across chemotherapy lines (means and 95 % confidence intervals)

EORTC QLQ-C30	Treatment phase						<i>p</i> value ^a
	First line <i>N</i> = 73	Post First line <i>N</i> = 38	Second line <i>N</i> = 63	Post second line <i>N</i> = 27	≥third line <i>N</i> = 47	Post ≥third line <i>N</i> = 22	
Physical functioning	76.0 (71.2–80.8)	70.5 (64.7–76.3)	71.1 (65.9–76.2)	65.2 (58.3–72.0)	62.5 (57.1–68.0)	53.2 (45.9–60.5)	<0.001
Role functioning	58.8 (52.7–65.0)	63.6 (55.9–71.3)	56.7 (49.9–63.5)	47.8 (38.6–57.0)	50.5 (43.5–57.6)	38.8 (29.0–48.7)	0.001
Social functioning	74.8 (69.4–80.1)	75.1 (68.2–81.9)	68.6 (62.6–74.6)	65.4 (57.3–73.6)	64.9 (58.7–71.1)	57.9 (49.2–66.6)	0.002
Emotional functioning	71.1 (66.4–75.7)	77.0 (71.2–82.8)	71.0 (65.9–76.1)	70.3 (63.4–77.2)	66.0 (60.7–71.4)	55.8 (48.4–63.1)	<0.001
Cognitive functioning	84.9 (80.4–89.3)	80.9 (75.4–86.4)	81.1 (76.3–86.0)	75.9 (69.4–82.4)	79.0 (73.9–84.1)	70.2 (63.3–77.1)	0.002
Global quality of life	61.6 (57.7–65.4)	65.3 (60.4–70.3)	59.0 (54.7–63.3)	57.3 (51.3–63.3)	50.0 (45.5–54.4)	44.2 (37.7–50.6)	<0.001

^a*p* value refers to the overall change over time

[partial] remission or stable disease) on the various QOL domains. We found that response (partial remission or stable disease) to treatment became significantly less frequent as the number of chemotherapy lines increased ($p < 0.001$). During first-line chemotherapy, only 18.7 % of the staging examinations indicated progressive disease, whereas this proportion substantially

increased during second-line (44.4 %) and third+ chemotherapy lines (62.5 %).

As expected, all differences were in favor of a response to treatment. The largest differences between patients with and without a treatment response were found for pain (19.0 vs. 37.2 points; difference 18.2 points) and appetite loss (17.4 vs. 32.7 points; difference 15.3 points). The other statistically

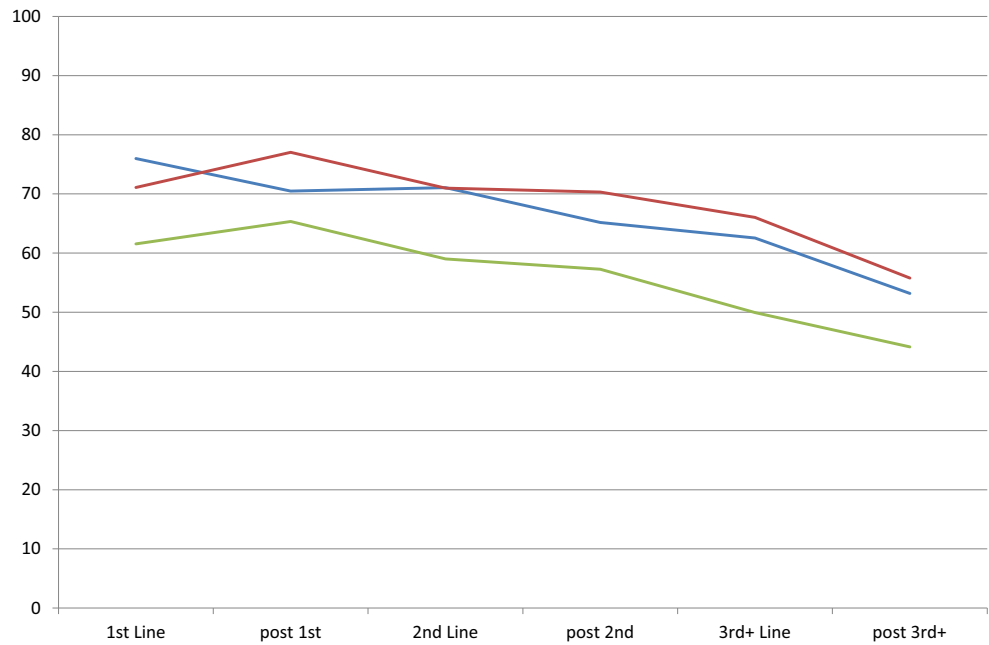
Table 3 EORTC QLQ-C30 symptom trajectories across chemotherapy lines (means and 95 % confidence intervals)

EORTC QLQ-C30	Treatment phase						<i>p</i> value ^a
	First line	Post first line	Second line	Post second line	≥third line	Post ≥third line	
Fatigue	40.0 (34.4–45.6)	39.1 (32.2–46.1)	46.1 (40.0–52.3)	49.6 (41.3–57.8)	53.7 (47.3–60.1)	61.5 (52.7–70.3)	<0.001
Nausea/vomiting	7.0 (3.7–10.3)	4.2 (0.0–8.6)	10.0 (6.1–13.9)	8.4 (3.0–13.9)	14.7 (10.8–18.6)	16.1 (10.2–22.1)	0.002
Pain	20.6 (14.8–26.3)	24.9 (17.5–32.3)	26.8 (20.3–33.2)	37.5 (28.7–46.4)	35.8 (29.1–42.4)	47.5 (38.0–57.0)	<0.001
Dyspnea	20.3 (14.4–26.2)	21.3 (13.8–28.7)	30.8 (24.2–37.3)	32.0 (23.1–40.9)	36.4 (29.6–43.2)	43.2 (33.7–52.7)	<0.001
Sleep disturbances	28.9 (22.8–34.9)	30.0 (22.4–37.6)	29.3 (22.6–36.0)	26.9 (17.9–35.9)	35.4 (28.5–42.3)	44.2 (34.7–53.8)	0.029
Appetite loss	20.0 (13.7–26.3)	17.6 (9.6–25.5)	25.8 (18.9–32.8)	29.8 (20.2–39.4)	35.0 (27.7–42.3)	48.0 (37.7–58.3)	<0.001
Constipation	19.4 (13.9–24.9)	15.2 (8.3–22.1)	21.8 (15.7–27.9)	26.7 (18.4–35.1)	18.6 (12.2–24.9)	21.7 (12.8–30.7)	0.269
Diarrhea	21.7 (16.3–27.0)	15.8 (8.7–22.9)	18.8 (12.6–25.0)	14.0 (5.3–22.8)	29.2 (22.9–35.4)	14.1 (4.5–23.6)	0.004
Financial impact	8.1 (3.8–12.3)	11.1 (5.9–16.4)	10.2 (5.5–14.8)	12.4 (6.3–18.5)	12.9 (8.1–17.8)	13.5 (7.1–20.0)	0.348
Taste alterations ^b	17.9 (12.7–23.0)	16.5 (9.8–23.1)	23.4 (17.6–29.2)	17.3 (9.2–25.4)	25.4 (19.5–31.3)	27.0 (18.2–35.8)	0.107

^a*p* value refers to the overall change over time

^b Additional scale calculated from two items from the EORTC item bank

Fig. 1 Physical functioning (blue), emotional functioning (red), and global quality of life (green) trajectories across chemotherapy lines



significant differences were <10 points: global QOL 9.2 points, fatigue 8.1 points, social functioning 7.9 points, physical functioning 7.7 points, dyspnea 6.4 points, role functioning 6.2 points, sleep disturbances 5.8 points, emotional functioning 5.4 points, nausea/vomiting 5.0 points, and cognitive functioning 3.7 points. Constipation, diarrhea, financial impact, and taste alterations were not found to be significantly associated with treatment response. None of the QOL scales exhibited a statistically significant interaction between treatment response and chemotherapy, which would have indicated a different association between treatment response and

QOL depending on the chemotherapy line. Further details are given in Table 4.

Conclusion

This is the first study to evaluate QOL across chemotherapy lines in unselected patients with nonresectable advanced CRC in clinical practice. Our data indicate that patients undergoing first- and second-line palliative chemotherapy experience stabilization of the global

Fig. 2 Fatigue (blue), pain (red), and appetite loss (green) trajectories across chemotherapy lines

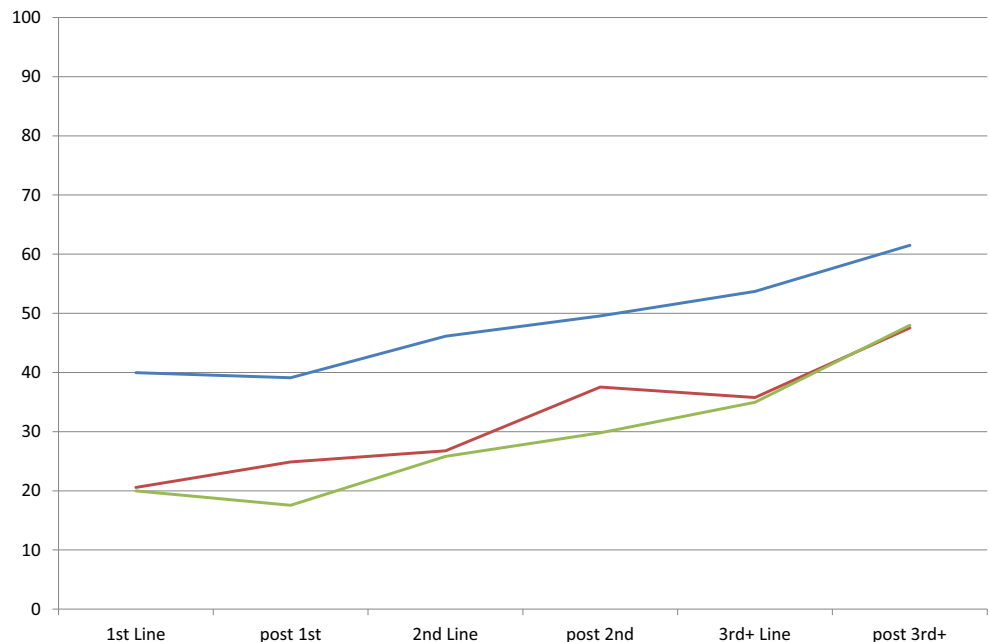


Table 4 EORTC QLQ-C30 scores and treatment response (means and 95 % confidence intervals)

EORTC QLQ-C30	Stable disease or (partial) remission	Progressive disease	
	<i>N</i> = 248	<i>N</i> = 228	
Physical functioning	72.3 (67.9–76.7)	64.6 (60.3–69.0)	<0.001
Role functioning	56.9 (51.0–62.8)	50.7 (44.9–56.5)	0.013
Social functioning	73.6 (68.3–79.0)	65.7 (60.4–71.1)	<0.001
Emotional functioning	74.7 (70.6–78.8)	69.3 (65.3–73.4)	0.002
Cognitive functioning	82.3 (78.4–86.9)	78.6 (74.4–82.7)	0.017
Global quality of life	63.5 (60.0–66.9)	54.3 (50.1–57.7)	<0.001
Fatigue	42.9 (37.7–48.0)	51.0 (45.9–56.0)	<0.001
Nausea/vomiting	6.9 (4.0–9.9)	11.9 (8.9–14.8)	0.004
Pain	19.0 (13.7–24.2)	37.2 (32.0–42.4)	<0.001
Dyspnea	23.7 (18.0–29.3)	30.1 (24.5–35.7)	0.009
Sleep disturbances	27.0 (21.1–32.9)	32.8 (26.9–38.6)	0.023
Appetite loss	17.4 (12.0–22.7)	32.7 (27.5–38.0)	<0.001
Constipation	17.0 (12.4–21.7)	19.9 (15.3–24.5)	0.198
Diarrhea	22.6 (17.6–27.6)	18.5 (13.6–23.5)	0.132
Financial impact	10.8 (6.3–15.3)	12.7 (8.3–17.2)	0.254
Taste alterations ^a	23.1 (18.3–27.9)	22.0 (17.2–26.8)	0.650

N number of staging time points

^a Additional scale calculated from two items from the EORTC item bank

QOL and psychosocial symptoms. Patients undergoing first- and second-line palliative chemotherapy, but not those undergoing third+ chemotherapy, showed stable QOL trajectories. The latter patients reported a substantially higher symptom burden. Similar results have been shown in a few other studies of patients with lung, pancreas, and biliary tract cancers [18–20]. Traditionally, objective end points such as response and survival rates have been used to evaluate the efficacy of chemotherapy in patients with advanced CRC. In recent years, increasingly more trials have incorporated HRQOL as a key end point. The American Society of Clinical Oncology claims that patient outcomes (toxicity, survival, and HRQOL) are more important than cancer outcomes (response rate and duration) [21].

We also investigated the association between our QOL data and the chemotherapy response, which was defined as disease stabilization or better on computed tomography scans every 3 months after starting chemotherapy. An improvement in nearly all QOL scales was shown in patients who achieved disease stabilization. The largest differences between patients with and without a treatment response were found for pain and appetite loss. Our data indicate that unselected patients who undergo treatment with several lines of chemotherapy and achieve a response to treatment benefit not only with regard to survival, as suggested by previous studies [22, 23], but also with regard to QOL.

Whereas the decrease in the number of patients across treatment lines reflected the survival rate in each patient group, we

also found a decrease in the proportion of patients who survived and completed the questionnaires. This should be noted as a limitation of our study affecting in particular our analysis of patients receiving three or more chemotherapy lines.

HRQOL is an important factor to consider when treating patients with cancer, especially those with metastatic disease. At the metastasis stage, it may be wiser to allocate resources to improving patients' HRQOL rather than investing in expensive and burdensome oncological treatments [24].

One of the major problems associated with assessing QOL during chemotherapy is the timing and frequency of the assessment. The optimal frequency of assessment remains unclear; however, when too much time elapses between two surveys, we cannot detect rapid and clinically important changes in QOL. Approximately 70 % of patients in clinical trials typically complete the baseline QOL measurements, but compliance with follow-up assessments is lower and missing data is a problem [25]. Compliance with QOL assessment in clinical trials that involve regular support from research staff may differ from that in clinical trials that involve routine QOL data collection in practice (e.g., in a busy oncology clinic). Collection of QOL data should become robust, inexpensive, easy, and readily interpretable. The present study showed that electronic questionnaire administration is a feasible way to collect QOL data in daily clinical practice.

Based on our findings, we recommend to assess QOL across the whole treatment trajectories and not just focus on single chemotherapy lines. Routine evaluation of HRQOL during administration of all chemotherapy lines would be optimal to obtain data for comparison of treatment options.

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Conflict of interest The authors declare that they have no competing interests.

References

1. Van Cutsem E, Nordlinger B, Cervantes A, Group EGW (2010) Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. *Ann Oncol* 21(Suppl 5):v93–v97
2. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D (1993) Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 306(6880):752–755
3. de Gramont A, Bosset JF, Milan C, Rougier P, Bouche O, Etienne PL, et al. (1997) Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 15(2):808–815
4. Douillard JY, Cunningham D, Roth AD, Navarro M, James RD, Karasek P, et al. (2000) Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 355(9209):1041–1047
5. Goldberg RM, Sargent DJ, Morton RF, Fuchs CS, Ramanathan RK, Williamson SK, et al. (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 22(1):23–30
6. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, et al. (2007) Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 25(12):1539–1544
7. Cunningham D, Humblet Y, Siena S, Khayat D, Bleiberg H, Santoro A, et al. (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351(4):337–345
8. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. (2011) Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. *J Clin Oncol* 29(15):2011–2019
9. Cella DF (1995) Measuring quality of life in palliative care. *Semin Oncol* 22(2 Suppl 3):73–81
10. Aaronson NK (1988) Quality of life: what is it? How should it be measured? *Oncology* 2(5):69–76 64
11. de Gramont A, Figuer A, Seymour M, Homerin M, Hmissi A, Cassidy J, et al. (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol* 18(16):2938–2947
12. Bennett L, Zhao Z, Barber B, Zhou X, Peeters M, Zhang J, et al. (2011) Health-related quality of life in patients with metastatic colorectal cancer treated with panitumumab in first- or second-line treatment. *Br J Cancer* 105(10):1495–1502
13. ESMO Guidelines Working Group, Van Cutsem EJ (2007) Advanced colorectal cancer: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 18(Suppl 2):ii25–ii26
14. Gehring K, Aaronson NK, Gundy CM, Taphoorn MJ, Sitskoom MM (2011) Predictors of neuropsychological improvement following cognitive rehabilitation in patients with gliomas. *J Int Neuropsychol Soc* 17(2):256–266
15. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. (1993) 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* 85(5):365–376
16. Osoba D, Rodrigues G, Myles J, Zee B, Pater J (1998) Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 16(1):139–144
17. Holzner B, Giesinger JM, Pinggera J, Zugal S, Schopf F, Oberuggenberger AS, et al. (2012) The computer-based health evaluation system (CHES): a software for electronic patient-reported outcome monitoring. *BMC Med Inform Decis Mak* 12(1):126

18. Koeberle D, Saletti P, Borner M, Gerber D, Dietrich D, Caspar CB, et al. (2008) Patient-reported outcomes of patients with advanced biliary tract cancers receiving gemcitabine plus capecitabine: a multicenter, phase II trial of the Swiss Group for Clinical Cancer Research. *J Clin Oncol* 26(22):3702–3708
19. Wintner LM, Giesinger JM, Zabernigg A, Sztankay M, Meraner V, Pall G, et al. (2013) Quality of life during chemotherapy in lung cancer patients: results across different treatment lines. *Br J Cancer* 109(9):2301–2308
20. Zabernigg A, Giesinger JM, Pall G, Gamper EM, Gatringer K, Wintner LM, et al. (2012) Quality of life across chemotherapy lines in patients with cancers of the pancreas and biliary tract. *BMC Cancer* 12:390
21. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines (1996) American Society of Clinical Oncology. *J Clin Oncol* 14(2):671–679
22. Glimelius B, Hoffman K, Graf W, Pahlman L, Sjoden PO (1994) Quality of life during chemotherapy in patients with symptomatic advanced colorectal cancer. The Nordic Gastrointestinal Tumor Adjuvant Therapy Group. *Cancer* 73(3):556–562
23. Au HJ, Karapetis CS, O'Callaghan CJ, Tu D, Moore MJ, Zalberg JR, et al. (2009) Health-related quality of life in patients with advanced colorectal cancer treated with cetuximab: overall and KRAS-specific results of the NCIC CTG and AGITG CO.17 trial. *J Clin Oncol* 27(11):1822–1828
24. Farkkila N, Sintonen H, Saarto T, Jarvinen H, Hanninen J, Taari K, et al. (2013) Health-related quality of life in colorectal cancer. *Color Dis Off J Assoc Coloproctol G B Irel* 15(5):e215–e222
25. Ganz PA, Gotay CC (2007) Use of patient-reported outcomes in phase III cancer treatment trials: lessons learned and future directions. *J Clin Oncol* 25(32):5063–5069