Annals of Oncology **10**: 775–782, 1999.
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Original article

Quality of life as subjective experience: Reframing of perception in patients with colon cancer undergoing radical resection with or without adjuvant chemotherapy

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Summary

Purpose and background: We examined whether patients with colon cancer undergoing surgery with or without adjuvant chemotherapy change the internal standards on which they base their quality-of-life (QL) estimation, and, if they do so, whether this reframing alters interpretation of QL findings. These questions were addressed within a randomized clinical trial of the Swiss Group for Clinical Cancer Research (SAKK 40/93).

Patients and methods: After radical resection of adenocarcinoma of the colon ($pT_{1-4}pN_{>0}M_0$ and $pT_{3-4}pN_0M_0$) and perioperative chemotherapy, patients were randomized to three treatment arms: observation only (A), 5-FU 450 mg/m^2 plus Levamisol (B), or 5-FU 600 mg/m^2 (C). QL was measured by linear analogue self-assessment indicators. Patients estimated their pre-surgery QL both before surgery and retrospectively thereafter, and their pre-adjuvant QL both at the beginning of randomly assigned chemotherapy or observation and retrospectively about two months later. Thereafter, current QL was assessed. Paired *t*-tests were used to test the hypotheses of no change.

Results: Overall, 187 patients with at least one pair of corresponding questionnaires were analyzed. Patients estimated their pre-surgery QL after surgery significantly lower than before and their pre-adjuvant QL under treatment or observation also lower than at the beginning. In the adjuvant phase, in contradiction to our hypothesis, chemotherapy had almost no impact on these changes attributed to reframing. Conventionally assessed changes indicated an improvement in QL. Patients with treatment C reported less improvement in functional performance than those with B or those under observation ($P = 0.04$). Patients with treatment B indicated a greater worsening in nausea/vomiting than those with C, whereas patients with observation only showed an improvement ($P = 0.0009$). After adjustment of current QL scores under treatment or observation to patients' retrospective estimation, the treatment effects were diluted but the overall improvement was substantially amplified in most QL indicators.

Conclusions: Patients with colon cancer substantially reframe their perception in estimating QL both under radical resection and under adjuvant chemotherapy or observation. This effect is an integral part of patients' adaptation to disease and treatment. An understanding of this phenomenon is of particular relevance for patient care. Its role in evaluating QL endpoints in clinical trials needs further investigation.

Key words: adjuvant therapy, colon cancer, quality of life, randomized trial, reframing, response-shift

Introduction

"Stories we understand are only badly told."
B. Brecht, Baal

As clinicians or healthy individuals we tend to compare a patient's current state of health with his or her state preceding the diagnosis. However, there is some evidence that patients with a chronic disease are 'reframing' their internal standards of health in the process of becoming and remaining ill. For example, a patient with bone metastases stating "I feel good" may live in a seriously impaired health status. 'Feeling good' may mean in this case "I am happy as long as it doesn't get worse".

Adopting the point of view of a sick person is particularly important for understanding the *subjective* experience of disease and treatment. The process of reframing may include an internal recalibration of, e.g., the meaning of 'good' physical functioning, but also a shift in personal values to a new understanding of what constitutes one's quality of life (QL) [1], e.g., the increasing importance of close relationships. This phenomenon has also been described as 'response-shift' and is used to interpret unexpected QL findings [2]. For example, patients with cancer and other chronic diseases, when assessed with generic scales, such as for psychological distress [3], show scores in the same range or even better than healthy individuals. Although an understanding of this phenomenon is of major importance for patient care and QL research it has rarely been studied [4].

We examined whether patients with newly diagnosed colon cancer change the internal standards on which they base their QL estimation, and, if they do so, whether this reframing alters interpretation of QL findings. These questions were addressed in regard to radical resection with perioperative chemotherapy and randomly assigned post-operative adjuvant chemotherapy or observation within a clinical trial of the Swiss Group for Clinical Cancer Research (SAKK 40/93).*

Based on clinical observation, we expected that patients' estimates of their pre-surgery QL would be lower after surgery compared to before. Patients tend to express an optimistic outlook after resection of the tumor (e.g., 'the cancer has been cured'). However, they also face surgical sequelae and are aware that it takes time to recover [5]. Adjusting to the fundamental changes in daily life provokes a shift in internal standards: Reframing the past toward worse QL would fit this enlarged experience and contribute to a favorable perception of the present. The motivation for this shift may be an understandable imperative to view one's condition in an optimistic light and to consider one's life worth living. This process may be termed mental homeostasis.

Similarly, we expected that the patients' retrospective estimates of their QL at the beginning of adjuvant therapy or observation would be lower than estimates made beforehand. This reframing was expected to be stronger in patients receiving chemotherapy compared to those without: experiencing cytotoxic side-effects would induce a greater shift in internal standards to regain mental homeostasis. The latter hypothesis was tested within the randomized trial design, and conventionally assessed changes were compared with those taking into account patients' reframing.

Patients and methods

The trial

The trial (SAKK 40/93) was open for all patients with radically resected and histologically proven adenocarcinoma of the colon with pathologically confirmed stages $pT_{1-4}pN_{>0}M_0$ and $pT_{3-4}pN_0M_0$. The patients had to have a potentially curative resection (R_0-resection) and no additional rectal carcinoma. The perioperative intraportal chemotherapy was a seven-day infusion of 5-fluorouracil (5-FU) starting immediately after surgery and interrupted by a two-hour infusion of mitomycin-C after the first 24 hours. It had to be stopped in case of serious toxicity. In case of technical problems with the recommended intraportal catheter, switching to the intravenous route was possible.

The randomization for post-operative adjuvant chemotherapy had to take place between 7 and 28 days after surgery, and was recommended 2 to 3 days before hospital discharge. The patients were assigned to three treatment arms: observation only (A); 5-FU 450 mg/m^2 i.v. once weekly for one year plus every second week 50 mg Levamisol orally every eight hours for three days (B); 5-FU 600 mg/m^2 i.v. once weekly for one year (C). Stratification included institution, age, tumor stage and administration of perioperative chemotherapy. Criteria for dose modifications were specified in the protocol. Toxicity was rated by physicians according to Early Clinical Trials Group guidelines.

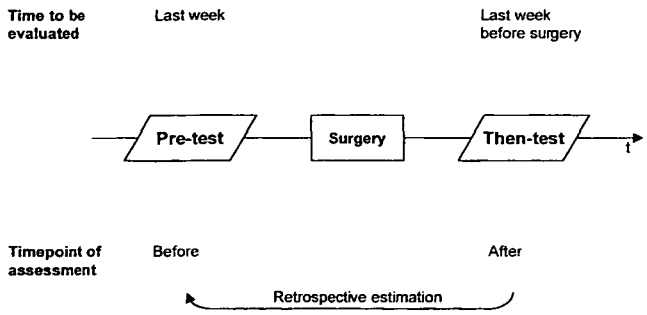

Figure 1. Quality of life assessment schedule regarding surgery.

The QL investigation was restricted to centers in German speaking areas of Switzerland, and to selected centers in Germany.

QL assessment

QL assessment included 15 linear analogue self assessment (LASA) [6] indicators of components of QL, ranging from 0–100. Global measures of well-being and functioning were complemented by specific measures of tumor symptoms and treatment side-effects. Responses on the global measures are expected to reflect the summation of the individual meaning and importance of various factors for each patient [7]. This property makes these measures suitable for studying reframing effects: The perception of a particular symptom and its relative importance may vary over time and on/off treatment [7].

We expected reframing to affect primarily physical measures and global measures associated with physical factors. The following seven indicators were prospectively defined as *primary endpoints*: physical well-being, mood, tiredness, coping/perceived adjustment [8], appetite, pain and overall QL. Functional performance, nausea/vomiting and anxiety were selected as secondary endpoints to assess common side-effects of 5-FU and of Levamisol, and to investigate consistency among complementary domains. Most of these indicators have been validated extensively [7, 9, 10] and used in various cancer sites [11–13].

As shown in Figure 1, patients were asked to estimate their pre-surgery QL both *before* surgery (surgery pre-test): "...We would like to know how you felt during the last week before your surgery or any other treatment...", and retrospectively *after* surgery (surgery 'then-test' [14]): "...Please think back a moment to the time before your surgery when you filled in the first questionnaire for us. Indicate on the enclosed questionnaire how you felt during the last week before your surgery...". The difference of the pre- and then-test was used as measure for reframing.

Both surgery pre- and then-test were assessed in the hospital after oral instruction of the patient by a physician or nurse, in addition to the written instruction indicated above. The surgery pre-test was to be assessed by all patients eligible for the clinical trial, regardless if they actually were randomized after surgery. The surgery then-test was to be completed on the day of randomization (i.e., close to hospital discharge). Sociodemographic data were also collected by the staff.

Similarly, following discharge, patients were asked to estimate their QL *at the beginning* of randomly assigned adjuvant chemotherapy or observation (adjuvant pre-test), as shown in Figure 2: "...Now that you are back at home, we would like to follow-up on how you are doing...", and retrospectively *about two months later* (adjuvant then-test): "...We are interested to find out what you now think about your well-being two months ago...". Finally, patients' *current* QL under treatment or observation (adjuvant post-test) was assessed about two weeks after the adjuvant then-test: "...Please respond to all questions regarding how you felt during the last week...". The adjuvant pre-test, then-test

* Part of these results were presented at the 21st Congress of the European Society for Medical Oncology, 1–5 November 1996, Vienna, Austria. Abstract published in Ann Oncol 1996; 7 (Suppl): 38.

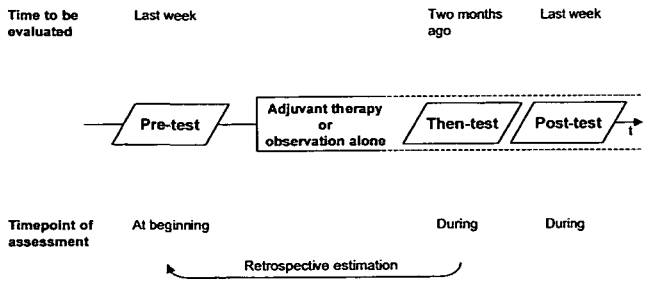

Figure 2. Quality of life assessment schedule regarding the adjuvant phase.

and post-test were completed at home. Questionnaires were sent to patients with a cover letter including the relevant instructions and a stamped addressed envelope to send it back to the coordinating center.

For all assessments, the time to be evaluated was also specified in the introductory statement to the questions on both pages of the questionnaire. For global QL the wording of the indicator was adjusted: The surgery pre-test: "How do you rate your quality of life *during the last week*", was phrased for the surgery *then-test*: "How do you rate your quality of life before the operation"; the adjuvant pre-test: "How do you rate your quality of life during the last week" was phrased for the adjuvant then-test: "How do you rate your quality of life during the time period approximately two months ago".

Statistical analysis

Submission rates of QL questionnaires were defined as the ratio of the number of received and evaluable questionnaires to the number of expected questionnaires in regard to various comparisons. The responders were compared with the non-responders regarding the biomedical and sociodemographic characteristics described in Table 1, separately for the comparisons related to surgery and the adjuvant phase.

The first hypothesis (i.e., worse scores of retrospective estimations) was investigated by paired *t*-tests between the pre- and then-test assessments separately for surgery and the adjuvant phase, the latter separately by treatment and overall. The second hypothesis (i.e., worse scores of retrospective estimations in patients with chemotherapy as compared to those without) was investigated by F-tests of changes between pre- and then-tests.

To control for factors with a potential impact on patients' perception of disease and treatment, the univariate analyses were complemented by multiple linear regression analyses. This analysis was explorative. The best predictive model was chosen using Mallow's C_p as criterion [15]. Biomedical factors included sex, age, family history of colorectal carcinomas, type of surgery, and lymph nodes involved (Table 1). For the comparison related to surgery, surgical and medical complications and duration of hospital stay were also included; for the comparison in the adjuvant situation, treatment assignment and the timing of QL assessment relative to the beginning of chemotherapy were used. Sociodemographic factors included education, professional position and living situation (Table 1). Finally, for both comparisons, institution, a well-known prognostic factor in colon cancer surgery, and the time interval between pre- and then-test were included.

Changes under adjuvant treatment or observation were conventionally investigated by paired *t*-tests between the pre- and post-test assessments separately by treatment and overall. In addition, patients' reframing was taken into account by comparing the post-test to the then-test instead of the conventional pre-test. To explore the discriminative capacity of these two approaches, weekly assessments of physician rated nausea and vomiting (5-point scales) over the first three months were used as an external criterion of a change induced by chemotherapy.

We faced ranges in timing of QL assessment going beyond the schedule defined in the protocol. However, we preferred to include all observations in the analysis instead of cutting the extremes. Timing of QL assessment can affect patient's self-estimation [16]. Therefore, we conducted additional analyses of the adjuvant then- minus pre-test, post- minus pre-test and post- minus then-test in a subsample with correct timing (n = 66) and investigated consistency. Patients fulfilling the following criteria were included: In cases assigned to arms B or C, the pre-test had to be filled in on day 1 of chemotherapy or within 21 days before; in all cases, the post-test had to be filled in within an interval of 54 to 96 days after the pre-test, and the time difference between then- and post-test had to be within 0 to 21 days.

Reframing effects (then- minus pre-test) and conventionally assessed changes (post- minus pre-test) may be correlated either positively or negatively depending on the magnitude and sign of post-test and then-test. To investigate this association, we calculated the Pearson correlation for each indicator.

A multiplicity problem arose due to tests performed on a series of QL scores on the same patients. We did not adjust for multiple testing because we did not rely on single p values but rather on patterns of statistical significance over a range of scores. Lines indicating 95% CI around observed mean effects help to assess visually such patterns irrespective of the amount of statistical significance. All tests were two-sided.

Table 1. Biomedical and sociodemographic patient characteristics of the total sample (n = 187).

Grouped categories	n[a] (%)
Sex	
Male	110 (59)
Female	77 (41)
Age	
<65	107 (57)
$\geqslant 65$	80 (43)
Family history of colorectal cancer	
Positive parents, grandparents, uncle, aunt, children/ other relatives	25 (14)
Negative	144 (77)
Not evaluable	17 (9)
Type of surgery	
Right hemicolectomy/resection of transverse colon/ sigmoid resection	124 (66)
Left hemicolectomy	45 (24)
Other[b]	18 (10)
Lymph node involvement	
pN_0	98 (53)
$pN_1/pN_2/pN_3$	86 (47)
Living situation	
With spouse or partner/with other(s)/alone with child(ren)	153 (83)
Alone	32 (17)
Educational level	
No training or certificate	40 (22)
Training or certificate/high school	112 (62)
Technical college/academic education	30 (16)
Last professional position	
Laborer/employee	56 (31)
Subordinate manager/administrative position/ self-employed small trade/farmer	69 (38)
Upper level manager/academic professional/director	27 (15)
Housekeeper without external job	30 (16)

[a] Sociodemographic data were available in 185 and complete in 182 cases.
[b] This category was not included in the regression analyses.

Table 2. Surgery and adjuvant pre-test scores.[a]

Indicator	Surgery		Adjuvant phase	
	n	Mean (SE)	*n*	Mean (SE)
Physical well-being	130	74 (2.1)	137	70 (1.9)
Functional performance	130	81 (2.0)	137	66 (2.3)
Tiredness	130	68 (2.3)	136	58 (2.2)
Pain	129	78 (2.2)	136	78 (2.0)
Appetite	130	77 (2.4)	137	78 (2.0)
Nausea/vomiting	129	89 (1.6)	137	91 (1.3)
Mood	130	58 (2.4)	137	69 (1.9)
Anxiety	128	58 (2.7)	128	71 (2.2)
Perceived adjustment	130	54 (2.6)	137	63 (2.4)
Global quality of life	129	71 (2.1)	135	68 (1.7)

[a] Secondary endpoints are in italics. All indicators range from 0–100. Higher scores indicate *better* QL (e.g., less pain) in all indicators.

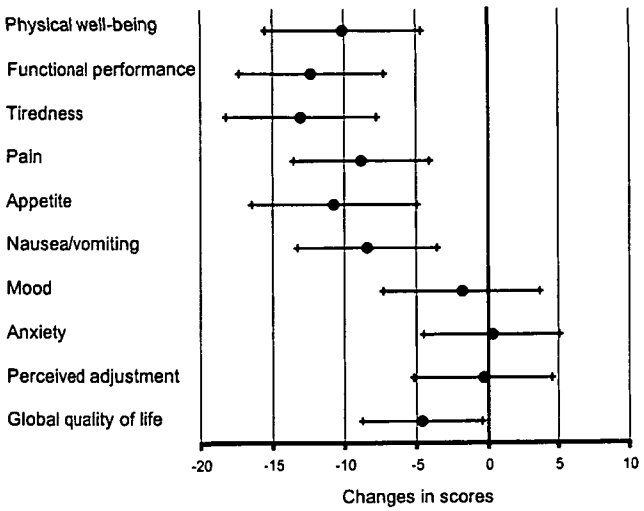

Figure 3. Reframing under radical resection and perioperative chemotherapy (n = 130). Negative differences between then- and pre-test (means with 95% CI) indicate worse scores of the retrospective estimation (then-test).

Results

Sample description

Overall, 215 patients were randomized in German speaking centers. For this investigation, 187 patients with at least one pair of corresponding questionnaires for either pre/then-test comparison were selected (87%). At the time of surgery, the main reason for missing QL data were administrative problems at the local centers (pre-test: 91%, then-test: 83% of all missing data). In the adjuvant phase, QL data was mainly missing due to patients' failure to send back the questionnaire (pre-test: 91%, then-test: 85%, post-test: 87% of all missing data).

Biomedical and sociodemographic characteristics are described in Table 1. In brief, 59% of the patients were male. The median age was 62 years, ranging from 27 to 88. Fourteen percent had a family history of colorectal carcinomas. The majority underwent standard surgical procedures. Fifty-three percent had no nodal involvement. Eighty-three percent lived with next of kin or friends. Seventy-eight percent had a formal professional education. A minority had an upper level or academic position. There was no major difference in these characteristics between the responders and the non-responders in the comparisons related to surgery and the adjuvant phase.

Reframing under surgery

Thirteen patients (7%) had surgery-related complications, 21 (11%) had complications related to perioperative chemotherapy, and 19 patients (10%) had other complications. Surgery pre- and then-test assessments were available in 132 patients (71%) of which 2 had missing clinical information and were excluded. The median time between the two assessments was 12 days (range 6–73 days), close to the duration of hospital stay (median 14 days, range 6–56 days). The surgery pre-test scores are shown in Table 2.

After surgery, patients estimated their pre-surgery physical measures (all $P < 0.0004$) and global QL ($P = 0.03$) significantly lower than before, as shown in Figure 3. The secondary endpoints showed consistent findings, with worse retrospective estimations of functional performance ($P < 0.0001$) and nausea/vomiting ($P = 0.001$). The significant changes among all indicators ranged from 4.6% (global QL) to 13% (tiredness) of full scale range.

Reframing under adjuvant therapy or observation

Adjuvant pre- and then-test assessments were available in 137 patients (74%). The median time between filling in the questionnaire at the beginning of adjuvant therapy or observation and the retrospective assessment was 50 days (range 13–80 days). Sixty-five percent of the patients receiving chemotherapy filled in the pre-test questionnaire before or at day 1 of chemotherapy (range −40–+45 days). The adjuvant pre-test scores are shown in Table 2; they did not significantly differ among the three treatment arms.

The changes between the assessment at the beginning of the adjuvant phase (pre-test) and the retrospective estimation (then-test) were not significantly affected by treatment, with the exception of appetite ($P = 0.03$), as shown in Figure 4. Patients under observation (arm A) reported retrospectively better appetite than they did before. Those receiving chemotherapy showed changes in the opposite direction. The bigger change in patients receiving 5-FU 450 mg/m^2 plus Levamisol (arm B) compared to those under observation was confirmed in the multivariate analysis (effect size = 13.8, $P = 0.003$).

Investigating the three treatment arms together, patients estimated their physical well-being ($P = 0.004$), mood ($P = 0.0002$) and global QL ($P = 0.003$) retrospectively lower than at the beginning of adjuvant therapy or observation (Figure 4). The secondary endpoints

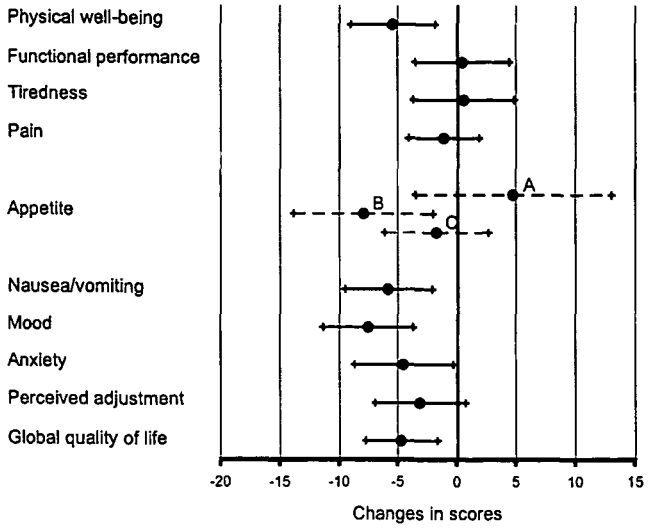

Figure 4. Reframing under post-operative adjuvant chemotherapy or observation (n = 137). Negative differences between then- and pre-test (means with 95% CI) indicate worse scores of the retrospective estimation (then-test) across treatments. Appetite is displayed by treatment arm: A refers to Observation only, B to 5-FU 450 mg/m^2 plus Levamisol and C to 5-FU 600 mg/m^2.

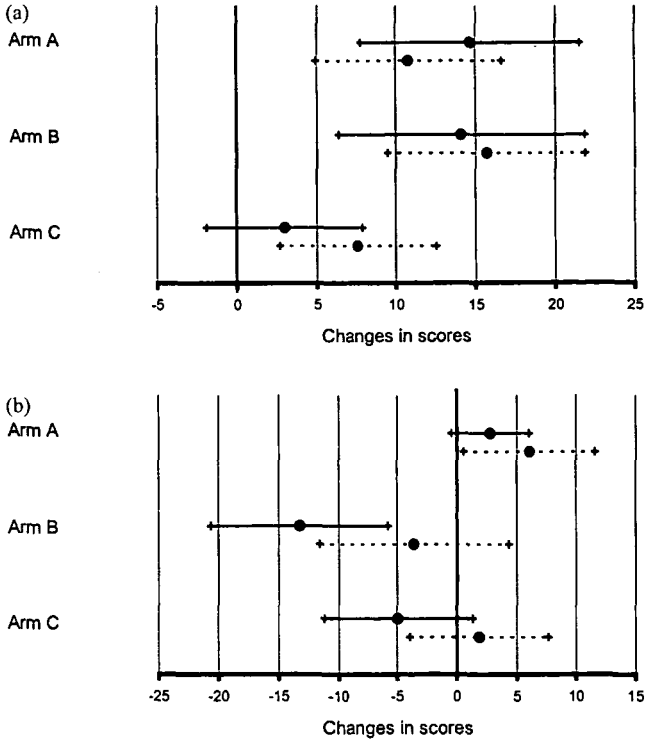

Figure 5. Changes of (a) functional performance (n = 128) and (b) nausea/vomiting (n = 129) by treatment relative to beginning of adjuvant treatment *versus* retrospective estimation. A refers to observation only, B to 5-FU 450 mg/m^2 plus Levamisol and C to 5-FU 600 mg/m^2. The solid lines refer to conventionally assessed changes (post- minus pre-test), the dashed lines to changes adjusted to patients' retrospective estimation (post- minus then-test): positive differences (means with 95% CI) indicate an improvement.

anxiety (P = 0.04) and nausea/vomiting (P = 0.003) similarly indicated worse retrospective estimations. The significant changes were considerably smaller than those under surgery and ranged from 4.5% (anxiety) to 7.5% (mood) of full scale range. In the subsample with correct timing (n = 66), the significant changes were consistently larger than those of the total adjuvant sample and ranged from 5% (global QL) to 9.3% (mood and anxiety) of full scale range.

Factors affecting reframing

The multiple linear regressions of the differences between then- and pre-test yielded no consistent pattern of biomedical or sociodemographic factors affecting reframing. Their impact varied among the QL measures and between the two situations. Under surgery, the investigated factors accounted for only 10%–15% of the variance of changes in four indicators (adj. R-squared), in the adjuvant situation, for 10%–13% in three indicators. This exploratory analysis did not change the interpretation of the univariate findings.

Changes relative to beginning of treatment versus retrospective estimation

Adjuvant pre- and then-test as well as post-test assessment were available in 132 patients (71%). The median time between the assessments of pre- and post-test was 64 days (range 21–143 days), and 14 days (range 0–93 days) between then-tests and the subsequent post-tests.

Based on conventionally assessed changes (post- minus pre-test), functional performance (P = 0.04) and nausea/vomiting (P = 0.0009) were the only measures with a statistically significant treatment effect, as shown in Figure 5. Patients under observation (arm A) and those receiving 5-FU 450 mg/m^2 plus Levamisol (arm B) reported an improvement in performance of about 15%, those with 5-FU 600 mg/m^2 (arm C) indicated a tendency only. Patients with B reported more worsening in nausea/vomiting than those with C, whereas patients under observation showed an improvement.

Patients' reframing was taken into account by comparing the assessment of current QL under treatment or observation (post-test) to the retrospective estimation (then-test) instead to the conventional assessment at the beginning of treatment (pre-test). This adjustment diluted the observed treatment effects (Figure 5). There was no indication that this adjustment would reveal a treatment effect in any of the remaining indicators. The subsample with correct timing showed consistent findings.

This finding was explored regarding nausea/vomiting, using physician ratings as an external criterion (arms B and C): In cases physicians observed at least once during the first three months nausea or vomiting of grade 2 or 3, patients indicated a greater worsening (post- minus pre-test) in the corresponding indicator (n = 13, mean change = −20.0, SE = 7.6) compared to those with grade 0 or 1 (n = 77, mean change = −8.5, SE = 2.6, P = 0.10). The adjustment to patients' retrospective estimation (post- minus then-test) diluted this effect: patients with grade 2 or 3 indicated similar changes (n = 16, mean

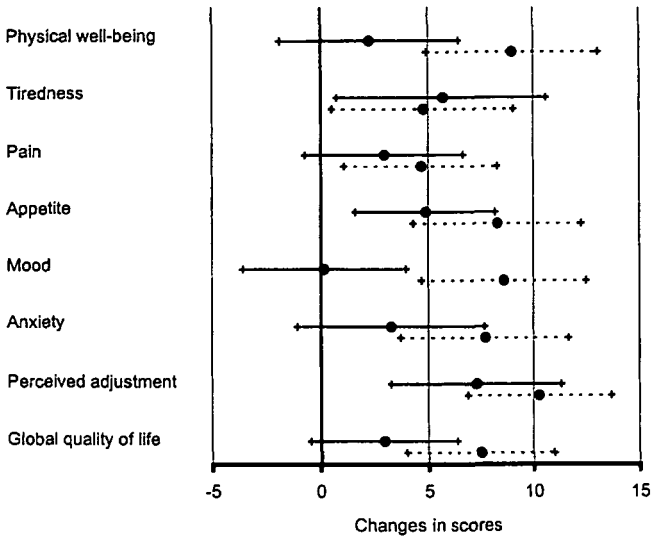

Figure 6. Changes across treatments relative to beginning of adjuvant treatment *versus* retrospective estimation (n = 132). The solid lines refer to conventionally assessed changes (post- minus pre-test), the dashed lines to changes adjusted to patients' retrospective estimation (post- minus then-test): positive differences (means with 95% CI) indicate an improvement.

change = 3.0, SE = 7.9) compared to those with grade 0 or 1 (n = 73, mean change = −0.9, SE = 2.8, P = 0.58).

The remaining indicators not significantly affected by treatment (post- minus pre-test) were investigated across treatment arms. As shown in Figure 6, patients indicated less tiredness (P = 0.02), better appetite (P = 0.004) and less efforts to cope (P = 0.0005) under adjuvant treatment or observation compared to the beginning. The significant changes ranged from 4.9% (appetite) to 7.3% (coping) of full scale range. After adjustment to patients' retrospective estimation (post- minus then-test), the overall improvement was substantially amplified in most indicators, as shown in Figure 6. The subsample with correct timing yielded consistent findings with larger changes than in the total adjuvant sample in both comparisons (post- minus pre-test, post- minus then-test) and in all indicators.

The conventionally assessed changes and those attributed to reframing (then- minus pre-test) were positively correlated in all indicators: The more the patients reframed their past QL towards better (worse) scores the greater the improvement (worsening) they reported over time. The correlations ranged from r = 0.35 for appetite (P = 0.0001) to r = 0.64 for functional performance (P = 0.0001).

Discussion

The question whether cancer patients change the internal standards on which they base their QL estimation has been debated for years. We addressed it within a randomized clinical trial. Based on clinical observations, we investigated reframing as a broad concept of changes in perception. We applied a specific theory founded measure, the then-test [14], to clarify whether this reframing actually amplifies treatment effects on perceived QL.

Our first hypothesis, that patients change their internal standards on which they base their QL estimation, is supported by our findings. Patients estimated their pre-surgery QL and especially physical measures after surgery *lower* than before, and their QL at the beginning of adjuvant therapy or observation retrospectively also *lower* than at that time. The findings regarding QL measures of complementary domains were mostly consistent. The fact that there were similar effects in two different clinical situations, regardless of hospital (surgery) or home assessment (adjuvant situation) and despite variation in timing of QL assessment, supports their validity.

Our second hypothesis, that cytotoxic side-effects would induce a greater shift in internal standards to regain mental homeostasis, was not supported. Reframing was not significantly affected by treatment, with the exception of appetite. Although it seems plausible that patients' reframing can be affected by a specific intervention, in the adjuvant situation reframing appears to be related more to patients' adaptation in a broader sense (i.e., diagnosis and surgical sequelae). The fact that reframing was not primarily induced by chemotherapy but was present to the same extent in the control group points into this direction.

Overall, based on conventionally assessed changes (post- minus pre-test), adjuvant chemotherapy had a modest impact on QL, as reported by others [17]. It has to be noted, however, that our sample is too small and the follow-up too short to address this question extensively. Across treatments, patients reported better scores in physical measures and less effort to cope at two months under adjuvant therapy or observation compared to the beginning. Coping emotionally with having colon cancer is a long-term process [5]. Patients indicated no change in mood or anxiety but a change in internal standard of these measures (then- minus pre-test). There can only be speculation whether this reframing precedes a forthcoming change also in emotional measures.

The question is, whether reframing effects contribute to our understanding of patients' QL in clinically relevant transitions. The significance of psychological adaptation is grounded to some extent on patients' ability to change their perception. Consequently, we compared QL scores under adjuvant therapy or observation (post-test) to patients' retrospective estimation (then-test) instead of the conventional assessment at the beginning of treatment (pre-test) [14]. This adjustment did dilute treatment effects. This finding was conclusive when using physician-rated nausea/vomiting as an external criterion. We expected the opposite. However, the adjustment did amplify the changes over time substantially. The pattern suggests that patients' experience over the first months may actually be different than documented by conventional changes.

How are these conflicting findings to be interpreted?

Howard et al. developed the then-test in healthy individuals [14]. They observed that participants in communication skills workshops altered their perception as a result of the intervention in a manner which contaminated self-assessment of the intervention (i.e., increased awareness). Howard et al. accounted for this response-shift by comparing scores after the intervention with retrospective estimations of the baseline (then-test) instead of the conventional baseline (pre-test) and were able to demonstrate the effect of the intervention. In cancer patients, this phenomenon is more complex. It is plausible that a change in perception is not primarily introduced by the intervention (e.g., treatment burden) but by coping with the disease itself. For most patients, living after being diagnosed with cancer is not the same as before. In contrast to disease- and surgery-related burden, cytotoxic side-effects are experienced mainly in their acute phase and, overall, may be less of a burden than the disease itself. These issues may explain why the adjustment of QL scores to the retrospective estimation amplified the changes overall but diluted the observed treatment effects, stressing the dominant impact of having cancer on QL. Similarly to this study, in patients receiving adjuvant therapy for breast cancer, chemotherapy (CMF) had an adverse but minor impact on QL compared to patients' adaptation following diagnosis and surgery [13].

It may be difficult for patients to estimate the past experience [18]. Reframing may reflect memory effects. Recall is not only dependent on time but also on the individual significance of disease and treatment. If poor memory were the only factor influencing the retrospective estimations, we would expect patients to report better and worse retrospective scores in roughly equal proportions. This was not the case, neither under surgery nor in the adjuvant phase. In other words, the *non-random* changes between pre- and then-tests cannot be interpreted by memory effects only. We could not check patients' understanding of the instructions or inquire into their thoughts when filling in the questionnaire in this multi-center trial. It has been shown that this type of instruction can reliably be given by oral communication [4]. In our trial, patients were orally instructed for the QL assessments related to surgery.

From a clinical point of view, our findings are in agreement with numerous case reports on patients' ability to adjust to the many limitations of disease and treatment. Providing patients with time perspective (e.g., duration of side-effects) may provoke reframing and thereby support adaptation both in situations of improvement and deterioration. Another well-known phenomenon of the way perception may change over time has been reported in terminally-ill cancer and AIDS patients. When things were going well, time was perceived as passing more quickly than when things were going badly [19]. Since reframing is obviously associated with adaptation, health care professionals need to consider this phenomenon.

Reframing effects are of relevance also for QL researchers. Our data give grounds to base the evaluation of QL on patients' *subjective* experience, complementary to but distinguished from concepts such as health status or functional disability. A patient's estimation of QL may alter in response to changes in disease or treatment, but it may also shift when there is little or no change in specific clinical factors. For example, anticipation of chemotherapy can have a substantial adverse impact on QL, as shown for adjuvant therapy in patients with breast cancer [13].

Considering adaptation, the relevance of population norms for QL measures and the definition of clinically meaningful changes both need attention. In essence, norms are based on the assumption of stable internal reference points and are often used in an absolute sense, as for example the Karnofsky index. Given that patients' subjective experience does change over time, and that reframing is one facet of this process, QL endpoints ideally reflect the weight of disease and treatment-related issues salient for each individual patient and situation [20].

Is the standard approach of assessing changes relative to baseline to be questioned? In our adjuvant setting, the adjustment of scores to the retrospective estimation did affect the interpretation of changes overall but reduced the effect of treatments. Our data suggest that the then-post-test does not invalidate the conventional pre-post-test but addresses a different question; conventional within-patient comparisons were mostly affected in magnitude but not in direction by reframing. In another study, patients with hairy cell leukemia indicated a disparity between toxicities while on *versus* off long-term therapy with interferon-α [21]. Their retrospective estimates of fatigue and performance status under treatment were also worse. In many studies based on conventional comparisons cytotoxic treatment has shown a smaller impact on QL than generally anticipated. The question is raised whether patients' current or retrospective estimation is more relevant for QL comparisons.

Further investigation is necessary to better understand this phenomenon in both curative and palliative situations, in relation to supportive interventions, in other chronic diseases and other QL measures. Regarding clinical trials, the discriminating capacity of conventional comparisons *versus* comparisons taking into account a measure of individual reframing needs to be clarified.

In conclusion, patients with colon cancer substantially reframe their perception in estimating QL indicators both under radical resection and under adjuvant chemotherapy or observation. This effect is an integral part of patients' adaptation to disease and treatment. An understanding of this phenomenon is of particular relevance for patient care. Its role in evaluating QL endpoints in clinical trials needs further investigation.

Acknowledgements

To study reframing of QL perception within a clinical trial needed considerable persuasiveness and logistic

efforts. In this sense we would like to thank the patients taking the time to complete the questionnaires, the data managers, nurses and surgeons taking care of this study in the centers, H. Gusset for central data management, and B. van Wegberg for study coordination at the beginning. We are grateful to M. Sprangers, A. Coates and A. Lowy for their critical comments on earlier drafts of this manuscript.

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Received 26 February 1999; accepted 7 June 1999.

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