# ORIGINAL ARTICLE \_\_

# Quality of life in colorectal cancer patients during chemotherapy in the era of monoclonal antibody therapies

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### Summary

**Purpose:** Colorectal cancer (CRC) survivors are currently living longer due to better therapies but they also need to maintain their quality of life (QoL). QoL is increasingly being used as primary outcome measure in clinical studies. This study was designed to gain knowledge about QoL during chemotherapy across different lines and different regimens.

**Methods:** The study comprised 101 CRC out patients receiving chemotherapy who completed the EORTC QLQ-C30 questionnaire. The Shapiro-Wilk, Kruskal-Wallis, and Mann-Whitney U tests were used for statistical analyses.

**Results:** The demographics of the patients were evaluated for QoL. Prior surgery, prior radiotherapy, working status, stage, comorbidity and sex had no effect on global health status in CRC patients, although some other demographics such as education, monthly income, age and type of chemotherapy regimen did have an effect on global health status. Role functioning was worse in older than in younger ones (p<0.05). Adjuvant chemotherapy did not affect the QoL scores negatively but palliative chemotherapy negatively affected the cognitive function, appetite loss and nausea/ vomiting scores (p<0.05). According to chemotherapy regimen, the best QoL was observed with adjuvant FUFA regimen. In the palliative setting FOLFOX/Bevacizumab was associated with the best QoL scores whereas FOLFIRI/Cetuximab were associated with the worst QoL scores.

**Conclusions:** Palliative chemotherapy maintained QoL irrespective of the chemotherapy line in metastatic CRC (mCRC) patients. Some demographics affect QoL and different chemotherapy regimens showed different QoL scores.

*Key words:* chemotherapy, colorectal cancer, quality of life, EORTC QoL C-30 Questionnaire

# Introduction

Cancer is a significant health problem which affects the QoL. Improving QoL is as important as survival prolongation. In the last 10 years, with the development of new anticancer drugs, it has become generally possible to prolong overall survival and more patients receive multiple treatment lines. Patients require not only chemotherapy administration, but they also need maintaining their QoL. The only effective treatment to improve QoL for mCRC is chemotherapy. Patients receiving different chemotherapy regimens and lines. In CRC, many drugs are being used for therapy. Drugs are divided into two groups: cytotoxic drugs and biological agents. In CRC these two groups are usually combined in mCRC and most patients are offered second and third line therapies when tumor progression or severe toxicity occurred with previous therapy.

### Quality of Life

According to the World Health Organization (WHO), definition of QoL is "An individual's perception of life, values, objectives, standards, and

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| C1-                                  |                          | NT              | Item | Version 3.0  |
|--------------------------------------|--------------------------|-----------------|------|--------------|
| Scale                                |                          | Number of items |      | Item numbers |
|                                      | Global health status/QoL |                 |      |              |
| Global health status / QoL (revised) | QL2                      | 2               | 6    | 29,3         |
|                                      | Functional scales        |                 |      |              |
| Physical functioning                 | PF2                      | 5               | 3    | 1 to 5       |
| Role functioning                     | RF2                      | 2               | 3    | 6,7          |
| Emotional functioning                | EF                       | 4               | 3    | 21 to 24     |
| Cognitive functioning                | CF                       | 2               | 3    | 20,25        |
| Social functioning                   |                          |                 |      |              |
|                                      | Symptom scales/ Items    |                 |      |              |
| Fatigue                              | FA                       | 3               | 3    | 10,12,18     |
| Nausea and vomiting                  | NV                       | 2               | 3    | 14,15        |
| Pain                                 | PA                       | 2               | 3    | 9,19         |
| Dyspnoa                              | DY                       | 1               | 3    | 8            |
| Insomnia                             | SL                       | 1               | 3    | 11           |
| Appetite loss                        | AP                       | 1               | 3    | 13           |
| Constipation                         | CO                       | 1               | 3    | 16           |
| Diarrhoea                            | DI                       | 1               | 3    | 17           |
| Financial difficulties               | FI                       | 1               | 3    | 28           |

#### Table 1. Scoring the QLQ-C30 version 3.0

interests in the framework of culture". Cancer patients experience problems such as "dyspnea, cough, hemoptysis, pain, fatigue, insomnia, loss of appetite, nausea, vomiting, diarrhea, constipation, weight loss, changes in urinary habits, anxiety, fear, depression, changes in body image, and impaired family and social relationships", all of which have adverse impact on QoL [1]. Chemotherapy causes side effects and toxicities on patients' emotional, physical, and spiritual well-being, whereas patients undergoing chemotherapy experience positive improvements in their QoL with respect to the chemotherapy regimen [2]. QoL can be assessed using more than 50 different instruments [3], most of which have been evaluated for reliability and validity for different nationalities [4]. The EORTC-QLQ-C30 was developed specifically for cancer patients and is a widely-used reliable instrument to measure QoL. QoL assessments studies may help to notice the effects of disease, different chemotherapy regimens and morbidities [2].

The aim of this study was to evaluate the QoL in CRC patients undergoing chemotherapy and to

explore the relationships between QoL and patient characteristics (age, gender, disease stage, comorbidities etc) and to evaluate the relationship of QoL with different chemotherapy regimens.

## Methods

#### Ethics statement

This research was approved by the Ethics Committee of 19 Mayis University, and informed oral consent was obtained from all participants prior to completion of the questionnaires.

#### Patients

This study was performed in the chemotherapy units of two tertiary referral hospitals. If the following criteria were met, patients were invited to participate:

- 1. CRC at any stage
- 2. ECOG performance status 0-2
- 3. Age 18 years or older
- 4. Received chemotherapy for at least 3 months Patients who completed the questionnaire were

| Characteristics       | Patients,<br>N | %    |  |
|-----------------------|----------------|------|--|
| Primary               |                |      |  |
| Colon                 | 65             | 64.3 |  |
| Rectum                | 36             | 35.6 |  |
| Stage                 |                |      |  |
| Ι                     | 0              | 0    |  |
| II                    | 9              | 8.9  |  |
| III                   | 20             | 19.8 |  |
| IV                    | 72             | 71.2 |  |
| Prior surgery         |                |      |  |
| Yes                   | 70             | 69.3 |  |
| No                    | 31             | 30.6 |  |
| Prior radiotherapy    |                |      |  |
| Yes                   | 21             | 20.8 |  |
| No                    | 80             | 79.2 |  |
| Chemotherapy setting  |                |      |  |
| Adjuvant              | 28             | 28   |  |
| Palliative            | 73             | 74   |  |
| Chemotherapy protocol |                |      |  |
| FUFA                  | 12             | 12   |  |
| FOLFOX+Cetuximab      | 15             | 15   |  |
| FOLFIRI+Bevacizumab   | 28             | 28   |  |
| FOLFOX                | 29             | 29   |  |
| FOLFIRI+Cetuximab     | 9              | 9    |  |
| FOLFOX+Bevacizumab    | 8              | 8    |  |
| Comorbidity           |                |      |  |
| Yes                   | 44             | 44   |  |
| No                    | 57             | 57   |  |

Table 2. Clinical and therapy characteristics (N=101)

included in the study since most chemotherapy regimens last about 6 months, it was decided to complete the questionnaires during the second half of the treatment to be able to better observe drug side effects. A total of 101 consecutive patients with CRC who were undergoing chemotherapy were included. Only few patients refused to participate because of their poor clinical condition. Symptom distress and the QoL of the patients were evaluated using the EORTC QLQ C-30 questionnaire. Personal, disease and therapy characteristics were retrieved from patient files. The following patient data were registered: age, gender, educational status, work status, income status, primary tumor site, chemotherapy drug, chemotherapy line, prior surgery/ radiotherapy and comorbid diseases. Confidentiality was guaranteed to the patients. Permission to use the questionnaires was obtained from EORTC Quality of Life Group.

#### Instruments

The standardized EORTC QLQ-C30 questionnaire was used to evaluate QoL in the current study. The QLQ C-30 includes 30 items that are divided into 3 main categories: global health status scale/QoL, functional scales and symptom scales (Table 1). A high score of QoL and a high score of functional scales show a good level, whereas a high score of symptom scale represents bad level. The questionnaire also contains 12 questions about sociodemographic features (gender, age, education, employment status, perceived income status) and the illness of the patient (diagnosis of cancer, stage of cancer, prior surgery, prior radiotherapy, anticancer therapy name and line). After the questionnaires were completed, they were checked to ensure that they had been fully completed.

### Statistics

Power analysis was performed before starting the study and the minimum sample size required was found to be 100 to evaluate possible significant differences. Statistical analyses were performed using SPSS software package, version 20. The questionnaire points were calculated according to the EORTC QLQ-C30 Scoring Manual. Compliance with the normal distribution of continuous variables was examined with the Shapiro-Wilk test. For comparison of normal distribution of the variables in 3 or more groups, the Kruskal-Wallis test was used and for comparison of two groups the Mann-Whitney U test was used. A p value less than 0.05 was accepted as significant in all the statistical analyses.

# Results

### Patient characteristics

The median patient age was 57.8 years and was similar between (neo) adjuvant and metastatic patients. Male patients predominated (58%). The majority of patients were married. Education level was low in most of the patients. The clinical characteristics of patients are shown in Table 2. All patients were receiving chemotherapy for CRC. More than half of the patients (64.3%) had colon cancer and the remaining (35.7%) had rectal cancer. As chemotherapy is not required in stage 1, there were no patients in the study at that stage. Stage 2 and 3 patients received only FUFA and FOLFOX chemotherapy. Irinotecan and biological agents were only used in stage 4 patients. The majority of the patients (71.2%) had stage 4 disease and were receiving anti-EGFR and anti-VEGF therapy combined with cytotoxic chemotherapy.



**Figure 1.** Results of the EORTC QLQC30 questionnaire (Europan Organisation for Research and Treatment of Cancer, Quality of Life Questionnaire, version 3,0). Indicated values are the mean of all pooled patients (N=101). QoL: quality of life, PF2: physical functioning, RF2: role functioning, EF2: emotional functioning, CF2: cognitive functioning, SF2: social functioning, FA: fatigue, NV: nausea and vomiting, PA: pain, DY: dyspnoea, SL: insomnia, AP: appetite loss, CO: constipation, DI: diarrhoea, FI: financial difficulties.

### Result of the questionnaires

The mean value of the global health status/ QoL was 56 points  $\pm 26.6$  standard deviation (SD). Within the functional scales, physical function (pf) was rated lowest with a mean score of  $61\pm 27.3$ points, whereas the cognitive function (cf) was rated highest with a mean of  $76\pm 25$  points. The most distinctive symptom was fatigue (fa) with a mean value of  $45\pm 28.5$  points, and the lowest was dyspnea with a mean value of  $14\pm 21$  points (Figure 1).

The patients were evaluated according to age and were divided into two groups (<65years and >65 years). The age of 65 was used as cut off, with the World Health Organization (WHO) definition of an older person. There was no significant difference in global health status (58 and 50 respectively, p=0.315) and symptom scales, but the role functioning was lower in older than in younger patients (76 and 58 respectively, p<0.05) (Table 3).

In this sample, 70 patients had undergone a palliative or a curative surgical operation and 31 had not. It was searched whether these procedures had affected the global health status/QoL, but no difference was found in scores between the patients who had or had not surgery (56 and 58.6 respectively; p>0.05).

The impact of radiotherapy on QoL was also investigated. Twenty one patients had received radiotherapy and 80 had not; no difference was observed between the two groups.

Comorbid diseases also did not cause any difference in QoL (p=0.066, narrowly missing statistical significance).

With respect to the relationship between

metastatic (N=29) and non-metastatic patients (N=72), there was no significant difference in global health status, but in functional scales the patients who were receiving adjuvant therapy showed better cognitive function (p<0.05). All the symptom scores were better in the adjuvant group but only nausea and vomiting and appetite loss were statistically significant (p<0.05). Although there were differences between the adjuvant and the palliative groups (Table 4) there was no change in metastatic patients during palliative chemotherapy, irrespective of chemotherapy line (Table 5). Patients who were receiving different chemotherapy regimens were compared for QoL (Table 6). Despite a similar global health status and functional scales, the dyspnea score was higher in the cetuximab (N=24) combination regimens than in the bevacizumab (N=36) combination regimens (p<0.05). Appetite loss score was lowest in the FUFA group and highest in the FOLFOX-+cetuximab group (p<0.05).

Patients were also divided into groups according to level of education and the results showed that there was a significant correlation between QoL and education level. Better scores were obtained from university degree patients with respect to nausea and vomiting symptoms than from lower education groups (p<0.05).

Income levels were classified in 3 levels as good, moderate and low. There was no difference in global health status but there were some differences in the symptom scales. For instance, the nausea and vomiting and appetite loss scores were worse in the low income group than in the others (p<0.05).

| Global health status             | Age <65 years | Age 65+ years               | p value |  |
|----------------------------------|---------------|-----------------------------|---------|--|
| QoL (mean±SD)                    | 58.09 ± 27.64 | 54.17 ± 24.50               | 0.315   |  |
| Median (range)                   | 58.33 (0-100) | 50.00 (0-100)               |         |  |
|                                  | Function      | al scales                   |         |  |
| Developed functioning (DE2)      | 65.41 ± 25.62 | 54.58 ± 29.88               | 0.077   |  |
| riiysicai functioning (FF2)      | 73.33 (0-100) | 63.33 (0-100)               | 0.075   |  |
| Dele functioning (DE2)           | 76.81 ± 30.14 | 58.85 ± 38.10               | 0.071*  |  |
| Role functioning (RF2)           | 83.33 (0-100) | 50.00 (0-100)               | 0.051*  |  |
| Emotional functioning (FF)       | 70.22 ± 29.48 | 68.75 ± 30.01               | 0.926   |  |
| Emotional functioning (EF)       | 75.00 (0-100) | 75.00 (0-100)               | 0.820   |  |
| Completions from objections (CD) | 75.85 ± 27.20 | $78.65 \pm 20.41$           | 0.0(1   |  |
| Cognitive functioning (CF)       | 83.33 (0-100) | 83.33 (0-100)               | 0.961   |  |
| Control from other in the (CF)   | 69,08 ± 29,19 | 70,31 ± 27,99               | 0.026   |  |
| Social functioning (SF)          | 66,67 (0-100) | 75,00 (0-100)               | 0.926   |  |
|                                  | Symptom so    | cales/items                 |         |  |
|                                  | 44.12 ± 29.11 | 48.61 ± 27.62               | 0.707   |  |
| Fatigue (FA)                     | 33.33 (0-100) | 44.44 (0-100)               | 0.587   |  |
|                                  | 19.81 ± 28.91 | 20.31 ± 24.95               |         |  |
| Nausea and vomiting (NV)         | 0 (0-100)     | 16.67 (0-100)               | 0.566   |  |
|                                  | 30.15 ± 30.91 | 30.15 ± 30.91 31.77 ± 30.92 |         |  |
| Pain (PA)                        | 16.67 (0-100) | 16.67 (0-100)               | 0.75    |  |
|                                  | 15.46 ± 27.16 | 12.50 ± 25.04               |         |  |
| Dysphoea (DY)                    | 0 (0-100)     | 0 (0-100)                   | 0.575   |  |
|                                  | 35.75 ± 33.97 | 32.29 ± 34.38               | 0.400   |  |
| insomma (SL)                     | 33.33 (0-100) | 33.33 (0-100)               | 0.602   |  |
| America loss (AD)                | 31.40 ± 36.55 | 40.63 ± 38.55               | 0.22    |  |
| Appetite loss (AP)               | 33.33 (0-100) | 33.33 (0-100)               | 0.22    |  |
|                                  | 30.43 ± 34.65 | 27.08 ± 36.35               | 0 517   |  |
| Constipation (CO)                | 33.33 (0-100) | 0 (0-100)                   | 0.515   |  |
|                                  | 25.49 ± 29.99 | 25.49 ± 29.99 33.33 ± 36.91 |         |  |
| Diarrnoea (DI)                   | 33.33 (0-100) | 33.33 (0-100)               | 0.595   |  |
|                                  | 42.03 ± 34.61 | 42.03 ± 34.61 37.50 ± 33.60 |         |  |
| Financial difficulties (FI)      | 33.33 (0-100) | 33.33 (0-100)               | 0.542   |  |

### Table 3. Age-related quality of life

# Discussion

Although gastrointestinal tumors represent a major health care problem worldwide, data for the QoL for patients suffering from this kinds of cancer are rare, especially data deriving from routine clinical practice [5]. QoL has become more important in health care practice and clinical researches [6]. Despite the importance of QoL evaluations, standardized methods are not applied in most oncology centers. In this study, a single, well-established and reliable assessment tool was used instead of several different specific questionnaires for patients. Despite the milder type and intensity of chemotherapy, elderly patients derive equivalent benefit compared with their younger counterparts [7]. Elderly patients showed similar QoL with the youngers in global health status, and only worse outcomes in role function were determined. Transportation to receive chemotherapy sessions may be more difficult in older patients and this may keep the elderly away from daily activities and hobbies. A history of surgical operation did not lead to any differences. Conditions affecting the QoL could be related to stoma but the stoma status was not evaluated because at the time of the current study the Turkish version of

| Global health status               | Metastatic           | Non-metastatic    | p value |  |
|------------------------------------|----------------------|-------------------|---------|--|
| QoL, mean±SD                       | 58.33 ± 20.54        | 56.28 ± 28.73     | 0.782   |  |
| Median (range)                     | 58.33 (8.33-100)     | 58.33 (0-100)     |         |  |
|                                    | Functional scales    |                   |         |  |
| Physical functioning (DF2)         | 67.14 ± 22.58        | 60.00 ± 28.89     | 0.419   |  |
| Physical functioning (PF2)         | 73.33 (6.67-100)     | 66.67 (0-100)     |         |  |
| Pole functioning (PP2)             | 71.43 ± 33.60        | $71.00 \pm 34.02$ | 0.962   |  |
| Role functioning (RF2)             | 83.33 (0-100)        | 83.33 (0-100)     |         |  |
| Emotional functioning (EE)         | $72.32 \pm 24.43$    | 68.75 ± 31.36     | 0.947   |  |
| Emotional functioning (EF)         | 75 (0-100)           | 75 (0-100)        |         |  |
| Compitized from attication of (CD) | 87.50 ± 14.79        | 72.60 ± 27.13     | 0.011   |  |
| Cognitive functioning (CF)         | 83.33 (50-100)       | 83.33 (0-100)     |         |  |
| Control from other in an (CD)      | 70.83 ± 25.51        | 68.95 ± 29.96     | 0.991   |  |
| Social functioning (SF)            | 75 (0-100)           | 66.67 (0-100)     |         |  |
|                                    | Symptom scales/items |                   |         |  |
|                                    | 39.29 ± 25.57        | 47.99 ± 29.48     | 0 1 7 1 |  |
| Faligue (FA)                       | 33.33 (0-100)        | 44.44 (0-100)     | 0.171   |  |
| Nousses and verticing (NN)         | $7.74 \pm 13.21$     | 24.66 ± 30.19     | 0.005   |  |
| Nausea and vointing (NV)           | 0 (0-50)             | 16.67 (0-100)     | 0.005   |  |
|                                    | $22.62 \pm 28.04$    | 33.80 ± 31.40     | 0.070   |  |
| Pain (PA)                          | 16.67 (0-100)        | 33.33 (0-100)     | 0.079   |  |
|                                    | $11.90 \pm 22.62$    | 15.53 ± 27.82     | 0.41    |  |
| Dysphoea (DY)                      | 0 (0-66.67)          | 0 (0-100)         | 0.01    |  |
|                                    | 32.14 ± 34.52        | 35.61 ± 33.94     |         |  |
| Insomnia (SL)                      | 33.33 (0-100)        | 33.33 (0-100)     | 0.01    |  |
| Appetite loss (AP)                 | 17.86 ± 27.94        | 40.64 ± 38.59     | 0.005   |  |
|                                    | 0 (0-100)            | 33.33 (0-100)     | 0.005   |  |
| Constinution (CO)                  | 23.81 ± 32.53        | 31.51 ± 35.96     | 0.77    |  |
| Constipation (CO)                  | 0 (0-100)            | 33.33 (0-100)     | 0.57    |  |
| Diamaka and (DI)                   | $22.62 \pm 31.47$    | 30.09 ± 32.70     | 0.241   |  |
| Diamioea (DI)                      | 0 (0-100)            | 33.33 (0-100)     | 0.241   |  |
| Financial difficultion (PI)        | 32.14 ± 32.05        | 43.84 ± 34.64     | 0117    |  |
|                                    | 33.33 (0-100)        | 33.33 (0-100)     | 0.117   |  |

**Table 4.** Quality of life in metastatic and non-metastatic patients

EORTC QLQ-CR29 (a specific module of CRC patients especially useful for stoma patients about sphincter control and sexual life) was not available. Patients were compared according to the stages of disease and differences were found in the cognitive function. Studies in literature have shown that depression is very common in metastatic cancer survivors [8]. This depressive mood may influence the cognitive functions negatively. In the adjuvant group, cognitive function, appetite loss and nausea/vomiting scores were better. These differences may primarily be related to impairments because of a longer time since diagnosis, disease progression and cumulative toxicity of drugs [9,10].

In the current study, there was no difference between different chemotherapy lines of metastatic patients (p>0.05). This means that palliative chemotherapy did not negatively affect QoL [10]. On the contrary, chemotherapy maintained the QoL. When deciding on further chemotherapy, we usually use ECOG performance status and ask a few brief questions to understand the tolerability potential of the patient. Actually, applying the questionnaire to every new patient provides more detailed information about the patient. Differences in QoL with different regimens may primarily be related to the type of chemotherapeutic drugs

| 1 st line2 ln line3 r lineQc, meansD52.89 + 27.980.019 + 31.38C2.22 + 23.57Median (range)52.89 + 27.980.67 (0.10)10.22 + 23.57Median (range)52.80 + 27.980.67.07 + 33.510.75.07 + 33.51Physcal functioning (PE)54.15 + 29.5275.35 + 20.0675.00 + 41.830.046.6766.67 (0.100)0.167 (0.100)0.100 (0.100)0.1670.167Another (INC)66.67 (0.100)0.167 (0.100)0.107 (0.103)0.167Another (INC)0.55 + 26.1375.00 + 41.830.1670.167Another (INC)0.167 (0.100)0.167 (0.100)0.167 (0.100)0.167 (0.100)Another (INC)0.167 (0.100)0.167 (0.100)0.155 (0.16.67)1.167 (0.100)Another (INC)0.167 (0.100)0.167 (0.100)0.167 (0.100)0.167 (0.100)Another (INC)0.167 (0.100)0.163 (0.100)0.167 (0.100)0.167 (0.100)Another (INC)0.167 (0.100)0.167 (0.100)0.167 (0.100)0.167 (0.100)Another (INC)0.167 (0.100)0.163 (0.100)0.167 (0.100)0.167 (0.100)Another (INC)0.167 (0.100)0.167 (0.100)0.167 (0.100)0.167 (0.100)Another (INC)0.167 (0.100) <td< th=""><th>Global Health Status</th><th>Palliative<br/>chemotherapy</th><th>Palliative<br/>chemotherapy</th><th>Palliative<br/>chemotherapy</th><th>p value</th></td<>  | Global Health Status           | Palliative<br>chemotherapy | Palliative<br>chemotherapy | Palliative<br>chemotherapy | p value |  |
|--|--------------------------------|----------------------------|----------------------------|----------------------------|---------|--|
| <table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-container><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row><table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-row></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container></table-container>   |                                | 1st line                   | 2nd line                   | 3rd line                   |         |  |
| Median (range)         50 (0-100)         66.67 (0-100)         79.17 (33.35-100)         0.137           Functional scales           Physical functioning (PF2)         54.15 ± 29.52         73.33 ± 0.096         67.78 ± 33.31         0.054           Role functioning (PF2)         56.65 ± 35.23         75.00 ± 41.85         0.137           G6.667 (0-100)         91.67 (0-100)         100 (0-100)         0.167           G6.667 (0-100)         91.67 (0-100)         100 (0-100)         0.167           G6.667 (0-100)         91.67 (0.33.31 (0.00)         0.167 (0.33.31 (0.00)         0.167           G6.735 ± 30.60         69.74 ± 27.30         77.78 ± 20.18         0.367           G6.67 (0-100)         83.33 (0-100)         83.33 (0-100)         83.53 (0-100)         80.44 ± 20.29         80.55 ± 20.70         0.562           Symptom scales/res   | <i>QoL,</i> mean±SD            | 52.89 ± 27.98              | 60.19 ± 31.38              | 72.22 ± 23.37              | 0.107   |  |
| Functional problem1415 2.9.573.35 2.9.0467.84 3.5.31Apple 1.5.2.5.3160.04.06.70Apple 1.5.3.5.1.00Apple 1.5.5.5.1.00Apple 1.5.5.5 | Median (range)                 | 50 (0-100)                 | 66.67 (0-100)              | 79.17 (33.33-100)          | 0.197   |  |
| Physical functioning (PE)54.15 ± 29.5273.33 ± 20.9667.78 ± 33.31<br>(80.78 ± 33.31)0.054Role functioning (RE2)65.65 ± 35.2684.26 ± 24.5775.00 ± 41.83<br>(100 (0.100))0.167Benotional functioning (RE2)66.67 (0.100)91.67 (0.100)100 (0.100)<br>(100 (0.100))0.167Benotional functioning (RE7)69.73 ± 27.7878.70 ± 27.3077.78 ± 20.18<br>(75.50 ± 100)0.333Cognitive functioning (RE7)69.73 ± 27.7878.70 ± 27.3077.78 ± 20.18<br>(75.50 ± 100)0.333Social functioning (SF)69.73 ± 27.7878.70 ± 27.3077.78 ± 20.18<br>(75.50 ± 100)0.333Fatigue (FA)55.71 ± 29.7475.65 ± 8.610.182<br>(75.50 ± 100)0.167Fatigue (FA)57.01 ± 29.7477.65 ± 28.503.333 ± 18.500.182<br>(75.50 ± 100)Path (FA)55.71 ± 29.7477.65 ± 28.503.533 ± 18.500.182<br>(75.50 ± 58.510.182Path (FA)57.01 ± 29.7477.65 ± 28.503.533 ± 18.500.182<br>(75.50 ± 28.510.182Path (FA)57.01 ± 29.7477.65 ± 28.503.533 ± 18.500.182<br>(75.50 ± 28.510.182<br>(75.50 ± 28.510.182<br>  |                                | Functior                   | nal scales                 |                            |         |  |
| Privide functioning (FP2)         66.67 (0-93.33)         73.33 (33.33-100)         80 (0-86.67)         0.034           Role functioning (RF2)         66.67 (0-100)         91.67 (0-100)         100 (0-100)         0.187           Emotional functioning (RF2)         66.67 (0-100)         91.67 (0-100)         100 (0-100)         0.187           Emotional functioning (RF)         66.67 (0-100)         83.33 (0-100)         91.67 (8.33-100)         0.367           Cognitive functioning (RF)         69.73 ± 27.78         78.70 ± 27.30         77.78 ± 20.18         0.367           Social functioning (RF)         66.67 (0-100)         66.67 (0-100)         91.67 (33.33-100)         0.367           Social functioning (RF)         66.67 (0-100)         66.67 (0-100)         91.67 (33.33-100)         0.52           Social functioning (RF)         50 (0-100)         44.44 (0-100)         33.33 (1.11-55.56)         0.103           Pain (PA)         35.03 (0-100)         35.33 (0-66.7)         22.22 + 40.37         0.673           Pain (PA)         35.33 (0-100)         35.33 (0-100)         55.5 + 8.61         0.182           Opspnoea (DY)         0 (0-100)         0 (0-66.67)         22.22 + 40.37         0.673           Opspnoea (DY)         0 (0-100)         35.33 (0-100)         35.33 (0-100)                           | Developed functioning (DE2)    | 54.15 ± 29.52              | 73.33 ± 20.96              | 67.78 ± 33.31              | 0.054   |  |
| <table-container>Rele functioning (RF2)65.65 ± 35.2684.26 ± 24.5775.00 ± 41.830.187Berlo functioning (EF)64.95 ± 32.6676.85 ± 26.1375.00 ± 34.560.377Brootional functioning (EF)69.75 ± 27.7878.70 ± 27.3091.67 (8.33-100)0.377Bognitive functioning (CF)69.75 ± 27.7878.70 ± 27.3077.78 ± 20.180.377Bognitive functioning (SF)67.55 ± 30.8069.44 ± 29.2980.56 ± 26.700.377Bognitive functioning (SF)66.70 (-100)66.67 (0-100)91.67 (33.33-100)0.512Bognitive functioning (SF)53.71 ± 29.7437.65 ± 28.5033.33 ± 18.590.103Bognitive functioning (SF)53.51 ± 26.700.1240.124Bognitive functioning (SF)16.67 (-100)16.67 (-100)5.56 (-16.67)Bognitive functioning (SF)14.91 ± 20.5222.22 ± 40.370.22.21 ± 10.21Bognitive functioning (SF)14.91 ± 20.5223.53 (-100)23.53 (-100)</table-container>   | riiysicai fulictiolillig (FF2) | 66.67 (0-93.33)            | 73.33 (33.33-100)          | 80 (0-86.67)               | 0.034   |  |
| Knick Hultchning (KP2)         66.67 (0-100)         91.67 (0-100)         100 (0-100)         0.137           Emotional functioning (EF)         64.93 ± 32.66         76.85 ± 26.13         75.00 ± 34.56         0.357           Cognitive functioning (CF)         69.75 ± 27.78         78.70 ± 27.30         77.78 ± 20.18         0.367           83.33 (0-100)         83.33 (0-100)         75 (50-100)         63.57 ± 0.08         69.44 ± 29.29         80.56 ± 26.70         0.552           Social functioning (SF)         66.67 (0-100)         66.67 (0-100)         91.67 (33.31 t0)         0.552           Fatigue (FA)         53.71 ± 29.74         37.65 ± 28.30         33.33 ± 18.59         0.103           Fatigue (FA)         50 (0-100)         44.44 (0-100)         33.33 (1.11-55.56)         0.182           Fatigue (FA)         24.15 ± 28.48         32.40 ± 56.81         5.55 ± 8.61         0.182           Nausea and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         0.222 (0-100)           Pain (PA)         37.50 ± 33.24         27.78 ± 21.39         22.22 ± 40.37         0.763           Opspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 (0-100)         0.666.70           Insomnia (SL)         39.46 ± 54.48         51.48 ± 352.8<                              | Pole functioning (DE2)         | 65.65 ± 35.26              | 84.26 ± 24.57              | $75.00 \pm 41.83$          | 0.187   |  |
| Bendtional functioning (EP)         64.93 ± 32.66         76.85 ± 26.13         75.00 ± 33.50         91.67 (8.33-100)         91.67 (8.33-100)           Cognitive functioning (CF)         69.73 ± 27.78         78.70 ± 27.30         77.78 ± 20.18         3.37           Cognitive functioning (SF)         67.35 ± 30.80         69.44 ± 29.29         80.56 ± 26.70         0.57           Social functioning (SF)         67.55 ± 30.80         66.67 (0-100)         66.67 (0-100)         0.167 (33.33-100)         75.71           Fatigue (FA)         55.71 ± 29.74         37.65 ± 28.30         35.33 ± 18.59         0.103           Mausea and vomiting (NV)         55.01 ± 20.74         37.65 ± 28.30         35.35 ± 8.61         0.182           Pain (PA)         75.05 ± 35.24         27.78 ± 21.39         22.22 ± 40.37         0.294           Mausea and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         55.6 (0-16.67)         22.22 (0-100)         0.94           Pain (PA)         35.35 (0-100)         35.35 (0-66.67)         22.22 (0-100)         0.94         9.94           Paysonea (DY)         16.97 ± 28.92         14.81 ± 20.52         22.22 (0-100)         0.94         9.94           Paysonea (DY)         16.97 ± 28.92         14.81 ± 35.28         16.67 ± 27.89         0.25                                 | Role functioning (RF2)         | 66.67 (0-100)              | 91.67 (0-100)              | 100 (0-100)                |         |  |
| Endudual functioning (EP)         75 (0-100)         83.33 (0-100)         91.67 (8.33-100)         0.337           Cognitive functioning (CP)         69.73 ± 27.78         78.70 ± 27.30         77.78 ± 20.18         0.367           Social functioning (SP)         67.35 ± 30.80         69.44 ± 29.29         80.56 ± 26.70         0.552           66.67 (0-100)         66.67 (0-100)         91.67 (83.33-100)         0.552           Fatigue (FA)         65.71 ± 29.74         37.65 ± 28.30         33.33 ± 18.59         0.103           Social functioning (NV)         44.15 ± 28.48         32.40 ± 36.81         5.55 ± 8.61         0.182           16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         2.22 ± 40.37         0.294           33.33 (0-100)         33.33 (0-66.67)         22.22 (0-100)         0.294           35.33 (0-100)         35.33 (0-66.67)         22.22 (0-100)         0.763           0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.763           0 (0-100)         35.33 (0-100)         35.33 (0-100)         26.67 (2-200 (0-200)         0.763           0 (0-100)         0 (0-66.67)         22.22 (0-103)         0.763         0.778         0.763           0 (0-100)         35.33 (0-100)         35.33 (0-100)         35.33 (0-1  | Emotional functioning (EE)     | 64.93 ± 32.66              | 76.85 ± 26.13              | $75.00 \pm 34.56$          | 0757    |  |
| <table-container>Cognitive functioning (CP)69.73 ± 27.7878.70 ± 27.3077.78 ± 20.180.36783.33 (0-100)83.33 (0-100)75 (50-100)0.36526.700.372Social functioning (SP)66.67 (0-100)66.67 (0-100)91.67 (33.33-100)0.562Symptom scales/temsSymptom scales/temsSymptom scales/temsSocial functioning (NP)53.71 ± 29.7437.65 ± 28.5033.33 ± 18.590.103Sign (FA)53.71 ± 29.7437.65 ± 28.5033.33 ± 18.590.103Social functioning (NP)24.15 ± 28.4832.40 ± 36.815.55 ± 8.610.18216.67 (0-100)16.67 (0-100)5.56 (0-16.67)2.220.29420.9333.33 (0-100)33.33 (0-66.67)2.22.20 ± 40.370.29416.67 (0-100)16.67 (0-100)5.56 (0-16.67)0.29420.9333.33 (0-100)33.33 (0-66.67)2.22.20 ± 10.370.29420.9314.97 ± 28.9214.81 ± 20.522.22.24 ± 40.370.76320.9314.97 ± 28.9214.81 ± 33.2816.67 ± 27.890.23720.9314.97 ± 28.9214.81 ± 33.2816.67 ± 27.890.23720.9433.33 (0-100)3.333 (0-100)16.67 (0-66.67)2.22.20 ± 10.2120.9433.33 (0-100)3.333 (0-100)3.333 (0-1002.22.20 ± 10.210.75820.9433.33 (0-100)3.333 (0-100)3.333 (0-1002.22.20 ± 3.330.10320.9514.94 ± 39.552.93 ± 29.27<td>Emotional functioning (EF)</td><td>75 (0-100)</td><td>83.33 (0-100)</td><td>91.67 (8.33-100)</td><td>0.557</td></table-container>   | Emotional functioning (EF)     | 75 (0-100)                 | 83.33 (0-100)              | 91.67 (8.33-100)           | 0.557   |  |
| Cognitive functioning (CF)         83.33 (0-100)         83.33 (0-100)         75 (50-100)         0.557           Social functioning (SF)         67.35 ± 30.80         69.44 ± 29.29         80.56 ± 26.70         0.552           Social functioning (SF)         66.67 (0-100)         66.67 (0-100)         91.67 (33.33-100)         0.552           Fatigue (FA)         53.71 ± 29.74         37.65 ± 28.50         33.33 ± 18.59         0.103           Social number scales/items         50 (0-100)         44.44 (0-100)         33.33 (1.11-55.56)         0.102           Nausea and vomiting (NV)         24.15 ± 28.48         32.40 ± 36.81         5.55 ± 8.61         0.182           16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         2.220 ± 40.37         0.294           201 (PA)         37.50 ± 35.24         27.78 ± 21.39         2.22.2 ± 40.37         0.294           35.33 (0-100)         35.33 (0-66.67)         2.2.20 (-100)         0.666           0 (0-100)         0 (0-66.67)         2.2.22 (0-100)         0.237           10 somnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           353.33 (0-100)         33.33 (0-100)         33.33 (0-100)         27.78 ± 25.09         0.648           35.33 (0-100)         33.33 (0   | Compiting functioning (CE)     | 69.73 ± 27.78              | 78.70 ± 27.30              | 77.78 ± 20.18              | 0767    |  |
| Social functioning (SF)         67.35 ± 30.80         69.44 ± 29.29         80.56 ± 26.70         0.552           66.67 (0-100)         66.67 (0-100)         91.67 (33.33 - 100)         0.552           Suppose colspan="3">Suppose colspan="3">Suppose colspan="3">Suppose colspan="3">Suppose colspan="3">Suppose colspan="3"           Ausee and vomiting (NV)         24.15 ± 28.48         32.40 ± 36.81         5.55 ± 8.61         0.182           Ausee and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         0.294           Ausee and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         0.294           Ausee and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         0.294           Ausee and vomiting (NV)         16.67 (0-100)         15.67 (0-100)         0.294           Ausee and vomiting (NV)         16.67 (0-100)         35.33 (0-100)         22.22 (0-100)         0.294           Ausee and vomiting (NV)         14.97 ± 28.92         14.81 ± 20.52         22.22 (0-100)         0.294           Ausee and vomiting (SL)         35.35 (0-100)         35.35 (0-100)         26.778 ± 25.09         0.424           Ausee and vomiting (SL)         34.69 ± 39   | cognitive functioning (CF)     | 83.33 (0-100)              | 83.33 (0-100)              | 75 (50-100)                | 0.307   |  |
| Social functioning (SF)         66.67 (0-100)         66.67 (0-100)         91.67 (33.33-100)         0.332           Symptom scales/items           Fatigue (FA)         53.71 ± 29.74         37.65 ± 28.30         33.33 ± 18.59         0.103           So (0-100)         44.44 (0-100)         33.33 (1.11-55.56)         0.182           Nausea and vomiting (NV)         24.15 ± 28.48         32.40 ± 36.81         5.55 ± 8.61         0.182           Pain (PA)         37.50 ± 33.24         27.78 ± 21.39         22.22 ± 40.37         0.294           J3.33 (0-100)         33.33 (0-66.67)         22.22 (0-100)         0.167           Dyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 (0-100)         0.232           Insomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Appetite loss (AP)         33.33 (0-100)         33.33 (0-100)         16.67 (0-66.67)         0.232           Constipation (CO)         0 (0-100)         33.33 (0-100)         27.78 ± 25.09         0.648           Marchea (DI)         35.33 ± 36.39         24.07 ± 25.06         22.22 ± 17.21         0.855           O (0-100)         33.33 (0-100)         23.23 (0-33.33)         0.100         23.22 (0-33.33)         0.100   | Social functioning (ST)        | 67.35 ± 30.80              | 69.44 ± 29.29              | 80.56 ± 26.70              | 0 550   |  |
| Symptom scallexitems           Fatigue (FA)         53.71 ± 29.74         57.65 ± 28.30         53.33 ± 18.59         0.103           50 (0-100)         44.44 (0-100)         53.33 ± 11.1 + 55.60         0.182           Nausea and vomiting (NV)         24.15 ± 28.48         52.40 ± 36.81         5.55 ± 8.61         0.182           Pan (PA)         16.67 (0-100)         16.67 (0-100)         5.66 (0-16.67)         0.294           Pan (PA)         37.35 (0-100)         53.35 (0-0.667)         22.22 ± 40.37         0.294           Pan (PA)         14.97 ± 28.92         14.81 ± 20.52         22.22 ± 40.37         0.763           Panen(AD)         0 (0-66.07)         22.22 (0-100)         0.294         0.294           Panen(AD)         0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.294           Panen(AD)         0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.294           Panen(AD)         35.33 (0-100)         35.33 (0-100)         16.67 (0-26.67)         0.292           Panen(AD)         35.33 (0-100)         35.33 (0-100)         27.88 ± 25.09         0.648           Panen(AD)         35.33 (0-100)         35.33 (0-100)         22.22 (0-33.31)         0.755           Panen(AD)         35.33 ±   | Social functioning (SF)        | 66.67 (0-100)              | 66.67 (0-100)              | 91.67 (33.33-100)          | 0.552   |  |
| Fatigue (FA)         53.71 ± 29.74         57.65 ± 28.30         53.33 ± 18.59         0.103           Fatigue (FA)         50 (0-100)         44.44 (0-100)         53.33 (1.11-55.56)         0.182           Nausea and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         0.294           Pain (FA)         57.50 ± 33.24         27.78 ± 21.39         22.22 ± 40.37         0.294           Pain (PA)         53.33 (0-100)         53.33 (0-66.67)         22.22 (0-100)         0.105           Paypnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 ± 40.37         0.763           O (0-100)         0 (0-66.67)         22.22 (0-100)         0.294         0.294           Magneti (SL)         59.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Mapetite loss (AP)         33.33 (0-100)         35.33 (0-100)         16.67 (0-66.67)         0.294           Appetite loss (AP)         33.33 (0-100)         35.33 (0-100)         27.78 ± 25.09         0.648           O (0-100)         35.33 (0-100)         27.22 (17.21)         0.855         0.075           O (0-100)         35.33 (0-100)         27.22 (0-33.33)         0.107         0.107           Diarrhoea (DI)         35.33 ± 36.39  |                                | Symptom s                  | scales/items               |                            |         |  |
| Fargue (A)         50 (0-100)         44.44 (0-100)         33.33 (1.1.1-55.56)           Nausea and vomiting (NV)         24.15 ± 28.48         32.40 ± 36.81         5.55 ± 8.61         0.182           16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         0.294           Pain (PA)         37.50 ± 33.24         27.78 ± 21.39         22.22 ± 40.37         0.294           Dyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 (0-100)         0           Dyspnoea (DY)         0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.294           Appetite loss (AP)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Appetite loss (AP)         33.33 (0-100)         33.33 (0-100)         16.67 (0-66.67)         0.294           Constipation (CO)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           O (0-100)         33.33 (0-100)         27.78 (0-66.67)         0.292         0.675           Diarrhoea (DI)         34.69 ± 39.65         25.93 ± 29.27         22.22 ± 17.21         0.855           O (0-100)         33.33 (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.755           Diarrhoea (DI)         33.33 ± 36.39         24.07 ± 25.06  |                                | 53.71 ± 29.74              | $37.65 \pm 28.30$          | 33.33 ± 18.59              | 0.103   |  |
| Nausea and vomiting (NV)         24.15 ± 28.48         32.40 ± 36.81         5.55 ± 8.61         0.182           16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)         22.22 ± 40.37         0.294           Pain (PA)         33.33 (0-100)         33.33 (0-66.67)         22.22 ± 40.37         0.763           Dyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 ± 40.37         0.763           0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.33.33 (0-66.67)         22.22 (0-100)           Insomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Appetite loss (AP)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           33.33 (0-100)         33.33 (0-100)         21.22 (0-33.33)         0.648         33.33 (0-100)         22.22 (0-33.33)           Ocnstipation (CO)         34.69 ± 39.65         25.93 ± 29.27         22.22 ± 17.21         0.855           0 (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.675         0.755           0 (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.755         0.755           0 (0-100)         33.33 (0-66.67)         22.22 (0-33.33)         0.755           0 (0-100)         <   | Fatigue (FA)                   | 50 (0-100)                 | 44.44 (0-100)              | 33.33 (11.11-55.56)        |         |  |
| Nausea and vomiting (NV)         16.67 (0-100)         16.67 (0-100)         5.56 (0-16.67)           Pain (PA)         37.50 ± 33.24         27.78 ± 21.39         22.22 ± 40.37         0.294           Jyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 ± 40.37         0.763           O (0-100)         0 (0-66.67)         22.22 (0-100)         0         0.667         22.22 (0-100)           Insomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Appetite loss (AP)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           33.33 (0-100)         33.33 (0-100)         27.78 (0-66.67)         0.648           35.33 (0-100)         35.33 (0-100)         27.78 (0-66.67)         0.855           O (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.755           O (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.755           O (0-100)         33.33 (0-66.67)         22.22 (0-33.33)         0.755           O (0-100)         33.33 (0-100)         23.23 (0-66.67)         22.22 (0-33.33)           Diarrhoea (DI)         35.33 (0-100)         35.33 (0-66.67)         22.22 (0-33.33)         0.439           Financial difficulties (FI)  |                                | 24.15 ± 28.48              | 32.40 ± 36.81              | 5.55 ± 8.61                | 0.182   |  |
| Pain (PA)         37.50 ± 33.24         27.78 ± 21.39         22.22 ± 40.37         0.294           33.33 (0-100)         33.33 (0-66.67)         22.22 (0-100)         0           Dyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 (0-100)         0.294           Insomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Appetite loss (AP)         33.33 (0-100)         33.33 (0-100)         16.67 (0-66.67)         0.237           Constipation (CO)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           33.33 (0-100)         33.33 (0-100)         27.78 (0-66.67)         0.855           O (0-100)         33.33 (0-100)         27.22 ± 17.21         0.855           O (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.175           Diarrhoea (DI)         33.33 ± 36.39         24.07 ± 25.06         22.22 ± 17.21         0.755           33.33 (0-100)         35.33 (0-66.67)         22.22 (0-33.33)         0.175           Financial difficulties (FI)         45.58 ± 35.81         44.44 ± 30.25         27.78 ± 38.97         0.439           33.33 (0-100)         50 (0-100)         27.78 (0-100)         0.439   | Nausea and vomiting (NV)       | 16.67 (0-100)              | 16.67 (0-100)              | 5.56 (0-16.67)             |         |  |
| Pain (PA)         33.33 (0-100)         33.33 (0-66.67)         22.22 (0-100)           Dyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 ± 40.37         0.763           0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.0237           1nsomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           Appetite loss (AP)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           33.33 (0-100)         33.33 (0-100)         23.33 (0-100)         27.78 (0-66.67)         0.855           Constipation (CO)         34.69 ± 39.65         25.93 ± 29.27         22.22 (0-33.33)         0.855           0 (0-100)         33.33 (0-100)         23.33 (0-100)         22.22 (0-33.33)         0.775           Diarrhoea (DI)         35.35 ± 36.39         24.07 ± 25.06         22.22 ± 17.21         0.775           33.33 (0-100)         33.33 (0-66.67)         22.22 (0-33.33)         0.775         0.439           Financial difficulties (FI)         45.58 ± 35.81         44.44 ± 30.25         27.78 ± 38.97         0.439           33.33 (0-100)         50 (0-100)         27.78 (0-100)         0.439         0.439         0.439  |                                | 37.50 ± 33.24              | 27.78 ± 21.39              | 22.22 ± 40.37              | 0.294   |  |
| Dyspnoea (DY)         14.97 ± 28.92         14.81 ± 20.52         22.22 ± 40.37         0.763           0 (0-100)         0 (0-66.67)         22.22 (0-100)         0.237           1nsomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           35.35 (0-100)         35.35 (0-100)         16.67 (0-66.67)         0.248           Appetite loss (AP)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           33.35 (0-100)         35.35 (0-100)         27.78 (0-66.67)         0.648           Constipation (CO)         34.69 ± 39.65         25.93 ± 29.27         22.22 ± 17.21         0.855           0 (0-100)         35.35 (0-100)         22.22 (0-33.33)         0.648           0 (0-100)         35.35 (0-100)         22.22 (0-33.33)         0.855           0 (0-100)         35.35 (0-100)         22.22 (0-33.33)         0.755           0 (D-100)         35.35 (0-100)         22.22 (0-33.33)         0.755           0 (D-100)         35.35 (0-66.67)         22.22 (0-35.35)         0.439           0 (D-100)         35.35 (0-66.67)         22.22 (0-35.35)         0.439           0 (D-100)         35.35 (0-100)         35.35 (0-100)         27.78 (0-100)   | Pain (PA)                      | 33.33 (0-100)              | 33.33 (0-66.67)            | 22.22 (0-100)              |         |  |
| Dysphoea (DY)         0 (0-100)         0 (0-66.67)         22.22 (0-100)           Insomnia (SL)         39.46 ± 34.48         31.48 ± 33.28         16.67 ± 27.89         0.237           33.33 (0-100)         33.33 (0-100)         16.67 (0-66.67)         0.237           Appetite loss (AP)         44.22 ± 41.04         35.19 ± 35.19         27.78 ± 25.09         0.648           33.33 (0-100)         33.33 (0-100)         27.78 (0-66.67)         0.648           Constipation (CO)         34.69 ± 39.65         25.93 ± 29.27         22.22 ± 17.21         0.855           0 (0-100)         33.33 (0-100)         22.22 (0-33.33)         0.775           Diarrhoea (DI)         33.33 (0-100)         33.33 (0-66.67)         22.22 (0-33.33)           Financial difficulties (FI)         45.58 ± 35.81         44.44 ± 30.25         27.78 ± 38.97         0.439           33.33 (0-100)         50 (0-100)         27.78 (0-100)         0.439   |                                | 14.97 ± 28.92              | 14.81 ± 20.52              | 22.22 ± 40.37              | 0.763   |  |
| Insomnia (SL)39.46 ± 34.4831.48 ± 33.2816.67 ± 27.890.23733.33 (0-100)33.33 (0-100)16.67 (0-66.67)44.22 ± 41.0435.19 ± 35.1927.78 ± 25.090.648Appetite loss (AP)44.22 ± 41.0435.19 ± 35.1927.78 (0-66.67)0.64833.33 (0-100)33.33 (0-100)27.78 (0-66.67)0.855Constipation (CO)34.69 ± 39.6525.93 ± 29.2722.22 ± 17.210.8550 (0-100)33.33 (0-100)22.22 (0-33.33)0.775Diarrhoea (DI)33.33 (0-100)33.33 (0-66.67)22.22 (0-33.33)Financial difficulties (FI)45.58 ± 35.8144.44 ± 30.2527.78 ± 38.970.43933.33 (0-100)50 (0-100)27.78 (0-100)0.439   | Dysphoea (DY)                  | 0 (0-100)                  | 0 (0-66.67)                | 22.22 (0-100)              |         |  |
| Insomina (SL)       33.33 (0-100)       33.33 (0-100)       16.67 (0-66.67)         Appetite loss (AP)       44.22 ± 41.04       35.19 ± 35.19       27.78 ± 25.09       0.648         33.33 (0-100)       33.33 (0-100)       27.78 (0-66.67)       0.648         Constipation (CO)       34.69 ± 39.65       25.93 ± 29.27       22.22 ± 17.21       0.855         0 (0-100)       33.33 (0-100)       22.22 (0-33.33)       0.648         Diarrhoea (DI)       33.33 ± 36.39       24.07 ± 25.06       22.22 ± 17.21       0.775         33.33 (0-100)       33.33 (0-66.67)       22.22 (0-33.33)       0.775         Financial difficulties (FI)       45.58 ± 35.81       44.44 ± 30.25       27.78 ± 38.97       0.439         33.33 (0-100)       50 (0-100)       27.78 (0-100)       0.439   | Incompie (CI.)                 | 39.46 ± 34.48              | 31.48 ± 33.28              | 16.67 ± 27.89              | 0.237   |  |
| Appetite loss (AP)       44.22 ± 41.04       35.19 ± 35.19       27.78 ± 25.09       0.648         33.33 (0-100)       33.33 (0-100)       27.78 (0-66.67)       0.648         Constipation (CO)       34.69 ± 39.65       25.93 ± 29.27       22.22 ± 17.21       0.855         0 (0-100)       33.33 (0-100)       22.22 (0-33.33)       0.648         Diarrhoea (DI)       35.35 ± 36.39       24.07 ± 25.06       22.22 ± 17.21       0.775         33.33 (0-100)       33.33 (0-66.67)       22.22 (0-33.33)       0.775         Financial difficulties (FI)       45.58 ± 35.81       44.44 ± 30.25       27.78 ± 38.97       0.439         33.33 (0-100)       50 (0-100)       27.78 (0-100)       0.439   | Insomnia (SL)                  | 33.33 (0-100)              | 33.33 (0-100)              | 16.67 (0-66.67)            |         |  |
| Appentie loss (AP)       33.33 (0-100)       33.33 (0-100)       27.78 (0-66.67)         Constipation (CO)       34.69 ± 39.65       25.93 ± 29.27       22.22 ± 17.21       0.855         0 (0-100)       33.33 (0-100)       22.22 (0-33.33)       0.855         Diarrhoea (DI)       33.33 (0-100)       33.33 (0-100)       22.22 (0-33.33)         Financial difficulties (FI)       45.58 ± 35.81       44.44 ± 30.25       27.78 ± 38.97       0.439         33.33 (0-100)       50 (0-100)       27.78 (0-100)       0.439   | Appetite loss (AP)             | $44.22 \pm 41.04$          | 35.19 ± 35.19              | 27.78 ± 25.09              | 0.648   |  |
| Second state         34.69 ± 39.65         25.93 ± 29.27         22.22 ± 17.21         0.855           0 (0-100)         33.33 (0-100)         22.22 (0-33.33)           Diarrhoea (DI)         33.33 ± 36.39         24.07 ± 25.06         22.22 ± 17.21         0.775           33.33 (0-100)         33.33 (0-66.67)         22.22 (0-33.33)         0.775           Financial difficulties (FI)         45.58 ± 35.81         44.44 ± 30.25         27.78 ± 38.97         0.439           33.33 (0-100)         50 (0-100)         27.78 (0-100)         0.775         0.775   |                                | 33.33 (0-100)              | 33.33 (0-100)              | 27.78 (0-66.67)            |         |  |
| 0 (0-100)       33.33 (0-100)       22.22 (0-33.33)         Diarrhoea (DI)       33.33 ± 36.39       24.07 ± 25.06       22.22 ± 17.21       0.775         33.33 (0-100)       33.33 (0-66.67)       22.22 (0-33.33)       0.775         Financial difficulties (FI)       45.58 ± 35.81       44.44 ± 30.25       27.78 ± 38.97       0.439         33.33 (0-100)       50 (0-100)       27.78 (0-100)       0.775  | Constipation (CO)              | 34.69 ± 39.65              | 25.93 ± 29.27              | 22.22 ± 17.21              | 0.855   |  |
| Diarrhoea (DI)         33.33 ± 36.39         24.07 ± 25.06         22.22 ± 17.21         0.775           33.33 (0-100)         33.33 (0-66.67)         22.22 (0-33.33)         24.07 ± 25.06         22.22 (0-33.33)         0.775           Financial difficulties (FI)         45.58 ± 35.81         44.44 ± 30.25         27.78 ± 38.97         0.439           33.33 (0-100)         50 (0-100)         27.78 (0-100)         27.78 (0-100)         27.78 (0-100)  |                                | 0 (0-100)                  | 33.33 (0-100)              | 22.22 (0-33.33)            |         |  |
| Diarmoea (D1)       33.33 (0-100)       33.33 (0-66.67)       22.22 (0-33.33)         Financial difficulties (FI)       45.58 ± 35.81       44.44 ± 30.25       27.78 ± 38.97       0.439         33.33 (0-100)       50 (0-100)       27.78 (0-100)   | Diamhana (DI)                  | 33.33 ± 36.39              | $24.07 \pm 25.06$          | 22.22 ± 17.21              | 0.775   |  |
| Financial difficulties (FI)         45.58 ± 35.81         44.44 ± 30.25         27.78 ± 38.97         0.439           33.33 (0-100)         50 (0-100)         27.78 (0-100)   | Dialifioea (DI)                | 33.33 (0-100)              | 33.33 (0-66.67)            | 22.22 (0-33.33)            |         |  |
| 33.33 (0-100)     50 (0-100)     27.78 (0-100)   | Financial difficulties (FI)    | 45.58 ± 35.81              | 44.44 ± 30.25              | 27.78 ± 38.97              | 0.439   |  |
|  | Financial unifculties (FI)     | 33.33 (0-100)              | 50 (0-100)                 | 27.78 (0-100)              |         |  |

Table 5. Quality of life between chemotherapy lines

or additional monoclonal antibodies. As far as we know, this is the first study about the effects of different chemotherapy regimens on QoL in patients with CRC. For example, even the treatment sequence of FOLFOX and FOLFIRI changes toxicity [11]. Bevacizumab-based therapy has been reported to have a more favorable toxicity profile with less severe diarrhea and neutropenia [5]. In the current study, treatment regimens with bevacizumab were also shown to yield better QoL and in contrast to the data reported by Unger et al., the QoL scores were worse with combinations of cetuximab [12].

Although no relationship has been demonstrated between education and QoL scores in several studies, a variation was observed in the current study at different levels of education in nausea/vomiting. The nausea/vomiting scores were lower in univpersity graduate patients than in others. Patients with higher levels of education are usually more aware of the effects of treatment and they might use antiemetics more regularly.

| Global<br>health<br>status   | FUFA              | FOLFOX+<br>Cetuximab | FOLFIRI+<br>Bevacizumab | FOLFOX          | FOLFIRI+<br>Cetuximab | FOLFOX +<br>Bevacizumab | p value |  |
|------------------------------|-------------------|----------------------|-------------------------|-----------------|-----------------------|-------------------------|---------|--|
| QoL,                         | 68.06 ± 18.06     | 55.56 ± 35.59        | 58.33 ± 27.69           | 51.15 ± 24.37   | 52.78 ± 20.83         | 62.5 ± 28.87            |         |  |
| mean±SD<br>Median<br>(range) | 66.67 (33.3-100)  | 50 (0-100)           | 54.17 (0-100)           | 50 (0-100)      | 50 (0-83.33)          | 62.5 (16.67-<br>100)    | 0.465   |  |
|                              |                   |                      | Function                | al scales       |                       |                         |         |  |
|                              | 72.22 ± 24.53     | 49.33 ± 34.07        | 63.81 ± 25.56           | 58.85 ± 26.25   | 63.70 ± 24.97         | 65.83 ± 25.06           | 0.10/   |  |
| PF2                          | 83.3 (6.7-100)    | 53.3(0-100)          | 70 (13,3-100)           | 66.7 (0-100)    | 73.3 (6.7-86.7)       | 73.3 (33.3-100)         | 0.106   |  |
|                              | 88.88 ± 24.96     | 61.11 ± 41.15        | 71.43 ± 32.67           | 66.67 ± 33.63   | 75.93 ± 34.47         | 72.92 ± 32.04           |         |  |
| RF2                          | 100 (16.7-100)    | 66.7(0-100)          | 83.3 (0-100)            | 66.7 (0-100)    | 100 (0-100)           | 83.3 (16.7-100)         | 0.322   |  |
|                              | 79.17 ± 22.33     | 58.93 ± 35.12        | 75.00 ± 28.60           | 68.10 ± 26.64   | 53.70 ± 34.64         | 80.21 ± 30.19           |         |  |
| EF                           | 87.5 (33.3-100)   | 62.5(0-100)          | 83.3 (0-100)            | 75 (0-100)      | 50 (8.3-100)          | 91.7 (8.3-100)          | 0.16    |  |
|                              | 87.50 ± 14.43     | 67.78 ± 31.79        | 73.21 ± 29.17           | 80.46 ± 23.18   | 77.78 ± 23.57         | 75.00 ± 12.60           |         |  |
| CF                           | 83.3 (50-100)     | 83.3(0-100)          | 83.3 (0-100)            | 83.3 (16.7-100) | 83.3 (33.3-100)       | 66.7 (66.7-100)         | 0.429   |  |
|                              | 81.94 ± 18.06     | 55.56 ± 34.31        | 71.43 ± 30.04           | 67.24 ± 27.63   | 70.37 ± 35.14         | 77.08 ± 12.40           |         |  |
| SF                           | 83,3 (33,3-100)   | 50(0-100)            | 75 (0-100)              | 66,7 (0-100)    | 66,7 (0-100)          | 75 (66,7-100)           | 0.303   |  |
|                              |                   |                      | Symptom so              | cales/items     |                       |                         |         |  |
|                              | 26.85 ± 24.83     | 51.85 ± 32.98        | 46.09 ± 31.98           | 47.13 ± 24.96   | 48.15 ± 26.06         | 51.39 ± 24.44           | 0.143   |  |
| ΓA                           | 22.2 (0-88.9)     | 55.5 (0-100)         | 33.3 (0-100)            | 44.4 (11.1-100) | 44.4 (11.1-100)       | 55.6 (0-88.9)           |         |  |
| NIV                          | $2.78 \pm 6.49$   | 17.78 ± 25.56        | 23.21 ± 28.45           | 21.26 ± 27.05   | 25.93 ± 35.46         | $27.08 \pm 36.67$       | 0 1 0 2 |  |
| INV                          | 0 (0-16.7)        | 16.7 (0-100)         | 16.7 (0-100)            | 16.7 (0-100)    | 16.7 (0-100)          | 8.3 (0-100)             | 0.172   |  |
| PΔ                           | $11.11 \pm 24.96$ | $41.11 \pm 40.76$    | 30.86 ± 31.25           | 33.33 ± 26.35   | 37.04 ± 32.03         | 22.92 ± 21.71           | 0.093   |  |
| IA                           | 0 (0-83.3)        | 33.3 (0-100)         | 16.7 (0-100)            | 33.3 (0-100)    | 33.3 (0-83.3)         | 16.7 (0-66.7)           | 0.075   |  |
| עס                           | 5.56 ± 19.25      | 31.11 ± 40.76        | 5.95 ± 15.85            | 18.39 ± 26.10   | 22.22 ± 28.86         | $4.17 \pm 11.79$        | 0.030*  |  |
| DI                           | 0 (0-66.7)        | 0 (0-100)            | 0 (0-66.7)              | 0 (0-100)       | 0 (0-66.7)            | 0 (0-33.3)              | 0.050"  |  |
| SL                           | $16.67 \pm 22.47$ | 51.11 ± 41.53        | 35.71 ± 35.05           | 34.48 ± 35.05   | $37.04 \pm 26.06$     | 25.00 ± 23.57           | 0 264   |  |
| SL                           | 0 (0-66.7)        | 33.3 (0-100)         | 33.3 (0-100)            | 33.3 (0-100)    | 33.3 (0-66.7)         | 33.3 (0-66.7)           | 0.204   |  |
| AP                           | $2.78 \pm 9.62$   | $46.67 \pm 39.44$    | 38.10 ± 43.24           | 35.63 ± 33.25   | $44.44 \pm 40.83$     | $29.17 \pm 27.82$       | 0.024   |  |
|                              | 0 (0-33.3)        | 33.3 (0-100)         | 33.3 (0-100)            | 33.3 (0-100)    | 33.3 (0-100)          | 33.3 (0-66.7)           | 0.024   |  |
| СО                           | 30.56 ± 36.12     | 35.56 ± 36.66        | 30.95 ± 32.62           | 27.59 ± 35.71   | 18.52 ± 33.79         | 29.17 ± 45.21           | 0.941   |  |
|                              | 33.3 (0-100)      | 33.3 (0-100)         | 33.3 (0-100)            | 0 (0-100)       | 0 (0-100)             | 0 (0-100)               | 0.041   |  |
| DI                           | $25.00 \pm 32.18$ | 28.89 ± 33.01        | 27.16 ± 32.08           | 24.14 ± 29.41   | 25.93 ± 27.78         | $50 \pm 47.14$          | 0.806   |  |
|                              | 16.7 (0-100)      | 33.3 (0-100)         | 33.3 (0-100)            | 0 (0-100)       | 33.3 (0-66.7)         | 50 (0-100)              |         |  |
| FI                           | 30.56 ± 33,21     | $60.00 \pm 40.24$    | 39.29 ± 35.20           | 36.78 ± 30.01   | 33.33 ± 28.87         | 45.83 ± 35.36           | 0.329   |  |
|                              | 33.3 (0-100)      | 66.7 (0-100)         | 33.3 (0-100)            | 33.3 (0-100)    | 33.3 (0-66.7)         | 50 (0-100)              | 0.527   |  |

Table 6. Six different chemotherapy regimens and correlation with QoL

For abbreviations see previous Tables

The results of this study showed a strong correlation between income level and nausea-vomiting, appetite loss and financial difficulties. Constant nausea causes difficulty in selecting food because some kinds of food exacerbate nausea. If an individual's income level is low it will be difficult to always find every kind of food he/she likes to eat and this may be the reason for appetite loss.

In our clinic, questionnaires about the pa-

tient's QoL are not used regularly. However, at the end of this study it was noticed that, according to the survey, a lot of patients with high pain and nausea/vomiting scores had received incomplete treatment for pain and emesis and therefore additional treatment was provided. A disadvantage of the study is the small number of patients for different types of chemotherapy regimens. Larger studies are surely needed, but the present study described the results of a particular region, ensuring the advantage of homogeneity.

In a study including gastric, CRC and pancreaticobiliary cancers, overall survival was compared in optimal and suboptimal chemotherapy groups, showing that patients with gastrointestinal cancers (especially CRC and gastric cancer) had better survival in the optimally-treated group [13]. In the current study we didn't evaluate survival but chemotherapy was mainly associated with a stable QoL over time, irrespective of treatment line and stage in CRC patients. Results of the GERGOR OPTIMOX 1 study showed that QoL has prognostic value in mCRC patients and QoL scores could give information to the clinician about the prognosis of a patient [14].

The decision of a chemotherapy regimen has been influenced by a number of factors, such as the patient's performance, comorbidities, k-ras status, resectability potential or desires [15]. Further treatments were seen to improve QoL and indirectly the survival in CRC patients and this may be encouraging for patients as there is still a social stigma attached to chemotherapy by a part of the society in Turkey.

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### References

- 1. Greenlee R, Murray T, Bolden S, Wingo PA. Cancer statistics. CA Cancer J Clin 2000;50:7-33.
- Akin S1, Can G, Aydiner A, Ozdilli K, Durna Z. Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. Eur J Oncol Nurs 2010;14:400-409.
- Feinstein AR, Josephy B, Wells CK. Scientific and clinical problems in indexes of functional disability. An Intern Med 1986;105:413-420.
- 4. Aaronson NK, Ahmedzai S, Bergman B 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;85:365–372.
- 5. Benoist C, Tournigand C, Andre T, de Gramont A. Therapeutic strategy in unresectable metastatic colorectal cancer. Ther Adv Med Oncol 2011;4:75-89.
- Testa MA, Simonson DC. Assessment of quality-of-life outcomes. N Engl J Med 1996;334:835-840.
- Bakogeorgos M, Mountzios G, Kotsantis G, Economopoulou P, Fytrakis N, Kentepozidis N. Chemotherapy compliance, tolerance and efficacy in elderly and non-elderly patients with metastatic colorectal cancer: a single institution comparative study. J BUON 2013;18:629-634.
- Low CA, Stanton AL. Activity Disruption and Depressive Symptoms in Women Living With Metastatic Breast Cancer. Health Psychol 2015;34:89-92.
- 9. Cruzado JA, Lopez-Santiago S, Martinez-Marin V, Jo-

se-Moreno G, Custodio AB, Feliu J. Longitudinal study of cognitive dysfunctions induced by adjuvant chemotherapy in colon cancer patients. Support Care Cancer 2014;22:1815-1823.

- Wintner LM, Giesinger JM, Zabernigg A et al. Quality of life during chemotherapy in lung cancer patients: results across different treatment lines. Br J Cancer 2013;109:2301-2308.
- 11. Walker MS, Pharm EY, Kerr J, Yim YM, Stephanski EJ, Shwartzberg LS. Symptom burden & quality of life among patients receiving second-line treatment of metastatic colorectal cancer. BMC Res Notes 2012;5:314.
- Unger K, Niehammer U, Hahn A et al. Treatment of metastatic colorectal cancer with cetuximab: influence on the quality of life. J Gastroenterol 2013;51:733-739.
- Uyeturk U, Turker I, Bal O et al. Treatment decision plans matter in elderly patients with gastrointestinal cancer: suboptimal or optimal? J BUON 2014;19:365-371.
- Diouf M, Chibaudel B, Filleron T et al. Could baseline health-related quality of life (QoL) predict overall survival in metastatic colorectal cancer? The results of the GERCOR OPTIMOX 1 study. Health Qual Life Outcomes 2014;12:69-81.
- 15. Rossi L, Vakiarou F, Zoratto F et al. Factors influencing choice of chemotherapy in metastatic colorectal cancer (mCRC). Cancer Manag Res 2013;5:377-385.