Quality of Life in Colon Cancer Patients Managed with FOLFOX Protocol

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Abstract

Background: The quality of life for patients treated with the FOLFOX protocol can vary depending on the stage of their cancer and how they respond to treatment. **Objectives:** The current study aimed to assess the quality of life (QoL) and adherence to treatment in a sample of Iraqi patients diagnosed with colon cancer and treated with FOLFOX protocol. **Patients and Methods:** A cross-sectional study was conducted at the Oncology Teaching Hospital, Al-Amal National Hospital for Oncology, and Al-Imamain Al-Kadhimiyan Medical City. Fifty adult patients with histologically proven colon cancer receiving treatment with the FOLFOX protocol were recruited for this research. The European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) and Morisky Medication-taking Adherence Scale (MMAS) were employed in this research. **Results:** It was observed that phlebitis 32 (64.0%) was the most common adverse event experienced after treatment with FOLFOX protocol, followed by neuropathy 27 (54.0%), nausea and vomiting 19 (38.0%), neutropenia 15 (30.0%), and diarrhea 12 (24.0%). Concerning participants adherence to treatment, according to MMAS-8 questionnaire, 27 (54%) had medium adherence and 19 (38%) had high adherence to treatment. Regarding the functional scales of EORTC QLQ-C30, role and emotional functioning were the most affected, with a lower mean than other scales. Among the symptoms scale of EORTC QLQ-C30; fatigue, nausea, vomiting, and appetite loss were the most distressing symptoms reported. **Conclusion:** Colon cancer's rising incidence underscores its significant impact on patients, affecting daily activities and emotional well-being. This extends to treatment modalities such as the FOLFOX protocol, potentially influencing patients' overall QoL.

Keywords: Colon cancer, EORTC QLQ-C30, FOLFOX, quality of life

Introduction

Colorectal cancer (CRC) is the third most common diagnosis and second deadliest malignancy for both sexes combined. CRC has both strong environmental associations and genetic risk factors. The incidence of new cases and mortality has been steadily declining for the past years possibly related to an increase in cancer screening and better therapy modalities, except for younger adults (younger than 50 years) in which the incidence rate increased by approximately 2% annually for tumors in the proximal and distal colon, as well as the rectum.[1] The change of the normal colonic epithelium to a precancerous lesion and ultimately an invasive carcinoma requires an accumulation of genetic mutations either somatic (acquired) and/or germline (inherited) in an approximately 10–15-year period.[2]

The United States Preventive Services Task Force recommendation to start screening at the age of 45 years for average risk population with high sensitivity stool-based methods every year, fecal immunochemical-DNA stool (FIT-DNA) testing every 1–3 years, colonoscopy every 10 years, CT colonography every 5 years, flexible sigmoidoscopy every 5 years, and flexible sigmoidoscopy every 10 years plus FIT every year.[3]

The patient's clinical features, tumor characteristics, and molecular profile (RAS/BRAF and microsatellite instability [MSI] status) should be considered during the treatment choice. A combination of chemotherapy (fluoropyrimidines and oxaliplatin) plus biological agents (antiepidermal growth factor

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receptor or antiangiogenic drugs) in addition to surgery, could give a chance of cure in resectable or potentially resectable tumors. About 20% of patients have synchronous metastases at diagnosis, frequently in the liver, and about 35% of patients develop metastases after a curative intent treatment.[4]

The FOLFOX protocol combines oxaliplatin, fluorouracil (5-FU), and leucovorin for the treatment of CRC. Oxaliplatin, a platinum-based chemotherapeutic, disrupts DNA function by forming cross-links, inhibiting replication and transcription, leading to cell death. Administered intravenously, it may cause adverse effects including systemic symptoms such as fever, nausea, and fatigue, as well as neuropathy and gastrointestinal issues. Contraindications include platinum hypersensitivity, severe neuropathy, renal impairment, and pregnancy. 5-FU, another component, inhibits DNA synthesis, primarily administered intravenously due to poor oral absorption. Common adverse effects include diarrhea and vomiting, while severe complications may include neutropenia and thrombocytopenia. Contraindications include dihydropyridine dehydrogenase deficiency and breastfeeding. Leucovorin, a derivative of folic acid, enhances 5-FU's effectiveness and can alleviate toxicity. Administered orally or intravenously, it may cause allergic reactions, with limited data on its safety during pregnancy. Overall, the FOLFOX protocol offers a comprehensive approach to CRC treatment, but careful monitoring and consideration of contraindications are essential for patient safety.[5-8] The current study aimed to assess the quality of life (QoL) and adherence to treatment in a sample of Iraqi patients diagnosed with colon cancer and treated with FOLFOX protocol.

Patients and Methods

Study design and settings

A cross-sectional study was conducted at Oncology Teaching Hospital (22 cases), Al-Amal National Hospital for Oncology (19 cases), and Al-Imamain Al-Kadhimiyan Medical City (9 cases) from February 1, 2022, to of December 1, 2022. Fifty patients diagnosed with colon cancer were recruited for this research.

Ethical issues

Ethical and scientific approval for the research was obtained from the Scientific Committee at the Department of Oncology, Iraqi Board for Medical Specialization. All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and or national research committee and with the 1964 Declaration of Helsinki and its later amendments. Verbal consent was obtained from all patients before starting data collection and after explaining the aims of the study and assuring confidentiality.

Study population

The study population were patients who received FOLFOX protocol for the treatment of colonic cancer attending one of the three medical centers mentioned above during the study period. A convenient sampling method was used to enroll the participants in this study.

Data collection

The researcher conducted data collection through direct interviews with potential patients and review of hospital records utilizing structured questionnaires. Sociodemographic characteristics such as age and sex were gathered, alongside the presence of adverse events including fatigue, diarrhea, nausea, vomiting, neuropathy, mucositis, and phlebitis. Hospital records provided data on complete blood count and cancer specifics such as staging and metastasis locations. Treatment adherence was evaluated using the Morisky Medication-taking Adherence Scale (MMAS), categorized into high, medium, and low adherence levels based on total scores. QoL assessment utilized the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaire (QLQ-C30), encompassing function-related scales, symptom-related scales/items, and global health status/QoL scale. Scoring involved estimating average item scores, transforming them into a scale ranging from 0 to 100, with higher scores indicating better functioning or higher symptom burden. The QLQ-C30 summary score was calculated as the mean of 13 scale and item scores, providing insight into overall QoL when all necessary data were available.

Inclusion criteria

Adult patients who were at least 18 years of age with histologically proven colon cancer receiving treatment with FOLFOX protocol and those who were able to provide informed consent were eligible to be included.

Exclusion criteria

Patients with comorbidities including neuropathy, and diabetes mellitus were excluded; patients who had a history of another type of tumor; and pregnant and breastfeeding women were excluded.

Outcome assessment

According to the chemotherapy-induced phlebitis severity scale,[9] two of the included patients in this study developed Grade 4 phlebitis, and thus, had to change to another treatment protocol. In addition, four cases experienced Grade 3 phlebitis and were managed with the insertion of Port-a-Cath. Neuropathy was classified according to the WHO severity scale.[10]

According to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE V5.0), anemia, neutropenia, nausea, diarrhea, constipation, and mucositis were graded according to their severity.[11]

Statistical analysis

Depending on whether the distribution was normal or skewed, continuous variables were expressed as means and standard deviations or medians with range. Categorical variables were expressed as frequency and percentages. R software packages (dplyr, gt_summary, and ggplot) were used for data processing, administration, and statistical analysis ("R

version 4.2.2, R Foundation for Statistical Computing, Vienna, Austria").

Results

Fifty participants with colon cancer were included in this study, the mean age was 54.2 ± 9.7 years old. The proportion of males was 66% and for females was 34%. The most common primary tumor location was in the sigmoid (28%) followed by cecum (18%) and ascending colon (12%). Twenty-two (44.0%) participants were from the Oncology Teaching Hospital, 19 (38.0%) from Al-Amal National Hospital for Oncology, and 9 (18.0%) from Al-Imamain Al-Kadhimiyan Medical City [Table 1].

Regarding the staging of the cancer, T3 was the predominant stage (38%), followed by cancer metastasis (32%) of the cases. The liver was the most common site of metastasis (75.0%) in this study, as shown in Table 2. It was observed that phlebitis (64.0%) was the most common adverse event experienced after treatment with FOLFOX protocol, followed by neuropathy (54.0%), nausea and vomiting (38.0%), neutropenia (30.0%), and diarrhea (24.0%). In regard to the neuropathy severity scale, it was observed the majority of cases experienced Grade 1 neuropathy (77.7%), while only 22.2% had Grade 2 neuropathy [Table 3]. In regard to the phlebitis severity scale, seven participants had a central line already inserted before treatment with FOLFOX protocol. Out of the remaining 43 cases, 19 (44.1%) developed Grade 2 phlebitis, 11 (25.5%) had Grade 0, and 7 (16.2%) had Grade 1, as shown in Table 4.

Concerning participants adherence to treatment, according to MMAS-8 questionnaire, 54% of the participants had medium adherence and 38% had high adherence to treatment [Table 5].

EORTC QLQ-C30 questionnaire assessment after treatment with FOLFOX protocol was carried out and it was found that the global health status has a mean of 65.8 ± 21.3. Regarding the functional scales of EORTC QLQ-C30, role and emotional functioning were the most affected, with a lower mean than other scales. Among the symptoms scale of EORTC QLQ-C30; fatigue, nausea, vomiting, and appetite loss were the most distressing symptoms reported [Table 6].

Table 1: Description of patient's demographics and cancer location

Characteristics	Cases (n=50[a])
Age (years)	54.2±9.7
Sex	
Males	33 (66.0)
Females	17 (34.0)
Tumor primary location	
Sigmoid	14 (28.0)
Cecum	9 (18.0)
Ascending colon	6 (12.0)
Splenic flexure	3 (6.0)
Descending colon	1 (2.0)
Transverse colon	1 (2.0)

[a]n (%)

Table 2: Staging of the colon cancer for the sample included in this study

	Cases (n=50[a])
Staging	
T3 N1	4 (8.0)
T3 N2	15 (30.0)
T4 N1	8 (16.0)
T4 N2	7 (14.0)
Metastasis	16 (32.0)
Liver	12 (75.0)
Liver + lung	4 (25.0)

[a]n (%)

Table 3: Description of adverse events

Side-effects	Cases (n=50[a])
Phlebitis	32 (64.0)
Neuropathy	27 (54.0)
Grade 1	21 (77.7)
Grade 2	6 (22.2)
Nausea and vomiting	19 (38.0)
Grade 1	16 (84.2)
Grade 2	3 (15.8)
Neutropenia	15 (30.0)
Grade 1	11 (73.3)
Grade 2	4 (26.6)
Diarrhea	12 (24.0)
Grade 1	11 (91.7)
Grade 2	1 (8.3)
Anemia	7 (18.0)
Grade 1	5 (71.4)
Grade 2	2 (28.6)
Constipation (grade 1)	5 (10.0)
Mucositis (grade 1)	3 (6.0)
Pain during oxaliplatin infusion	3 (6.0)
Hand foot syndrome	1 (2.0)

[a]n (%)

Discussion

Colon cancer is one of the cancers that stand at the top of the list for the most common and deadliest malignancies worldwide, being the third most common diagnosis and second most fatal malignancy. This along with increasing incidence in the younger population[1] necessitates a thorough analysis for a better understanding of the cancer itself as well as its treatment. As mentioned by Comella *et al*., Conroy *et al*., and Chen *et al*.,[12-14] a large proportion of patients with colon cancer are suffering from a wide spectrum of symptoms that can negatively affect their QoL. Such symptoms might be attributed, in part, to the disease itself and the medications used in its treatment; of which chemotherapeutic agents constitute a major component.

Table 4: Description of phlebitis severity scale

Phlebitis Severity Scale	Cases ($n=43^a$)
Grade 0: None	11 (25.5)
Grade 1: Mild	7 (16.2)
Grade 2: Moderate	19 (44.1)
Grade 3: Marked	4 (9.3)
Grade 4: Severe	2 (4.6)

[a]*n* (%)

Table 5: Morisky Medication-taking Adherence Scale-8 item level of adherence to treatment

MMAS-8	Cases ($n=50^a$)
High adherence	19 (38.0)
Medium adherence	27 (54.0)
Low adherence	4 (8.0)

[a]*n* (%). MMAS-8: Morisky Medication-taking Adherence Scale 8 item

Table 6: Quality of life for patients on FOLFOX protocol

EORTC QLQ-C30 domain	Cases ($n=50^a$)
Global health status/QoL	65.8±21.3
Functional scales	
Physical functioning	71.1±19.03
Role functioning	69.9±25.3
Emotional functioning	65.1±12.4
Cognitive functioning	78.2±25.1
Social functioning	75.2±28.1
Symptom scales	
Fatigue	62.2±19.3
Nausea and vomiting	45.0±22.1
Pain	19.5±8.3
Dyspnea	13.8±6.4
Insomnia	27.3±16.2
Appetite loss	39.9±20.3
Constipation	25.6±18.2
Diarrhea	32.1±13.7
Financial difficulties	48.0±21.3

QoL: Quality of life, EORTC QLQ-C30: European Organization for Research and Treatment of Cancer QoL questionnaire-C30, [a]Mean ± SD

FOLFOX and XELOX (xeloda + oxaliplatin) are the two most used combination chemotherapy regimens, which were found to be equally effective in controlling the disease.[12,15] Therefore, the process of determining which regimen to use has depended on other factors, one of those factors was evaluating the patient's QoL using a specific scoring system; as we did in our current study examining the QoL in a sample of patients on FOLFOX treatment protocol.

Our patients were found to be younger (mean age of 54 years) than those included in a study in France[13] and another in Taiwan[16] (mean age of 65 and 75 years, respectively). This might be related, in part, to the higher life expectancy among the population of those countries. Male patients were found to constitute about two-thirds of our sample, this is in concordance with Comella *et al*., Conroy *et al*., and Chen *et al*.[12-14]

Patients with their primary tumor at the left-sided colon (splenic flexure, descending colon, and sigmoid) were found to slightly outnumber those with right-sided cancer (cecum, ascending, and transverse colon) in our study (36% vs. 32%, respectively). This is similar to what Kumar *et al*.[17] had. Comella *et al.*, Conroy *et al*., Chen *et al*., and Lin *et al*.[12-14,16] classified the tumor location into colonic versus rectal cancer, with the predominance of colonic cancer.

Using the American Joint Committee on Cancer (AJCC) TNM system,[18] most of our patients were at Stage III disease (68%), with the remaining one-third having a Stage IV metastatic disease. The liver was observed as the most common site for metastasis (75% of metastatic cases). Sánchez-Gundín *et al*.[19] had similar results to ours with two-thirds of their sample having Stage III disease. Hochster *et al*.[20] results agreed with ours regarding the most common site for distant metastasis as being the liver (76%).

Regarding the side effects of FOLFOX regimen as depicted by our study. Phlebitis was the most common adverse effect, observed in 64.0% of the participants. Venous adverse events were so severe that two of the participants had to change to another treatment protocol and four had managed with insertion of Port-a-Cath. The most probable explanation for this high prevalence is the oxaliplatin-induced peripheral vascular pain, fluorouracil-induced-phlebitis, and the absence of venous central line. This had been confirmed by Matsuoka *et al*.[21] study in which they evaluated vascular pain in patients with CRC receiving peripheral venous chemotherapy with or without oxaliplatin and concluded that peripheral venous administration of oxaliplatin chemotherapy induces vascular pain in patients with colon cancer, irrespective of blood vessel diameter. Díaz-Rubio *et al*.[22] similarly mentioned venous complications among FOLFOX-induced adverse effects, with 4% of their patients recorded with such events, of them deep vein thrombosis was reported and related to FOLFOX treatment.

Neurotoxicity (neuropathy) was the second most common adverse effect, observed in more than half of our participants (54%). Most of them reported Grade 1 neuropathy with mild paresthesia and/or decreased deep tendon reflexes. Unsurprisingly peripheral neuropathy has been well-known as a side effect of oxaliplatin therapy.[23] A similar result was obtained by Comella *et al*.,[12] and Díaz-Rubio *et al*.,[22] and Cassidy *et al*.[24] reported an even higher figure (80%), of whom (17%) suffered intolerable paresthesia. On the other hand, Hochster *et al*. and Porschen *et al*.[20,25] had less than one-quarter of their participants with neuropathy. This might be related to the presence of certain factors that influence the occurrence of neuropathy, factors like the number of chemotherapy cycles and the duration over which the medication is infused have been suggested by Wiela-Hojeńska *et al*.[23]

Less than half of our patients experienced chemotherapy-induced hematological reactions (anemia and neutropenia). This is in

concordance with what Hochster *et al*.[20] had. Nonetheless, Comella *et al*. and Díaz-Rubio *et al*.[12,22] reported that up to (80%) of their study sample had such reactions. This, in turn, urged some studies by Hochster *et al*., Cassidy *et al*., and Porschen *et al*.[20,24,25] that compared FOLFOX therapy to other treatment regimens that were found to be associated with a much lower risk of hematotoxicity, of those, is the XELOX regimen where 5-fluorouracil was replaced by capecitabine.

Other reactions encountered by our participants including gastrointestinal manifestations (nausea, vomiting, diarrhea, and constipation), mucositis, and hand-foot disease were identical to what Comella *et al*., Hochster *et al*., Díaz-Rubio *et al*., Cassidy *et al*., and Porschen *et al*. reported in their studies.[12,20,22,24,25]

As part of the data collected to help analyze the QoL in colon cancer patients, we assessed the adherence of our patients to their cancer treatment (FOLFOX therapy) using the MMAS-8 adherence scale.[26,27] The most common pattern of adherence identified in our participants was moderate (54%) followed by high (38%) and adherence (8%) had low adherence which might be attributed, in part, to the impact of side effects.

On the other hand, Seal *et al*.[28] compared adherence to IV chemotherapeutic regimens (FOLFOX) versus oral regimens using the medication possession ratio (MPR).[29] They reported a high overall adherence, with adherence to IV medication being better than that toward oral medication.

Besides, another study by Díaz-Rubio *et al*.[22] assessed adherence by quantifying the number of patients who were able to complete 10 or more cycles of FOLFOX regimen and found that (66%) of their overall study sample were able to fulfill that definition. Moreover, they suggested that factors such as gender, overall health, and disease stage might contribute to patients' adherence to their treatment.

It is worth mentioning that having used different methods for assessing adherence, makes it difficult to compare the results of those studies. In addition, we could not find other studies examining the adherence to FOLFOX protocol using the MMAS-8 adherence scaling.

The primary aim of our study is to assess and analyze the QoL in colon cancer patients so that our work would contribute to the ongoing effort to help understand and minimize the suffering of such population.

Out of 100 points, with 100 being the best possible QoL and zero being the worst, our sample patients reported average global health. This is similar to what Comella *et al*.,[12] Conroy *et al*.,[13] Chen *et al*.,[14] Lin *et al*.,[16] and Sánchez-Gundín *et al*.[19] found (scores ranging from 60 to 75).

On the functional scale, all five areas of function were within average in our participants, with cognitive being the best functional area and emotional functioning being the least favorable. A study in France[13] also showed similar results. However, higher scores have been recorded by Chen *et al*., Lin *et al*., and Sánchez-Gundín *et al*.[14,16,19] across the five areas of functioning post-FOLFOX therapy. The fact that those studies included patients with nonmetastatic and lower-stage colon cancer (most patients with Stage II and Stage III disease) might contribute to such scores.

In addition, some studies assessed the patients' QoL before and after the administration of chemotherapy which could further clarify whether the medications would have an effect, and the type of that effect, on the QoL. One study by Lin *et al*.[16] involved elderly Taiwanese patients with nonmetastatic colon cancer and observed some degree of improvement in the functional scales following chemotherapy administration in comparison to the baseline scores.

On the symptom scale, fatigue was the most bothersome symptom among our patients, while dyspnea was the least annoying. Among gastrointestinal symptoms, nausea and vomiting were the worst. Besides, financial problems had an observable impact. Although fatigue was found to be the most disabling symptom among patients in nearly all available studies by Comella *et al*., Conroy *et al*., Chen *et al*., Lin *et al*., and Sánchez-Gundín *et al*.,[12-14,16,19] overall, much lower scores (and thus less bothersome symptoms) were reported by their participants.

Even though the same scoring system has been used by all the aforementioned studies to evaluate the QoL; given its subjective nature, highly variable responses are expected. This might put a reasonable explanation for what we have observed. Furthermore, other confounding factors could play a role in the generation and progression of those symptoms. For instance, the overall duration of treatment and the number of chemotherapy courses might affect the occurrence and severity of symptoms as shown by Lin *et al*.[16] Many other factors still need evaluation such as the patient's age, gender, and disease stage as potential contributors to the participant's symptomatology and QoL.

A study in southern Italy by Comella *et al*.[12] including 164 patients, reported that (79%) of their participants had deterioration in symptoms, defined as a drop of 10 points or more from the baseline score, after 24 weeks of treatment. This could be one example of the adverse effect chemotherapeutic medications might have on colon cancer patients' QoL.

Conclusion

Colon cancer imposes a significant burden on patients, impacting daily life, emotional and cognitive well-being, and treatment experiences, notably with the FOLFOX protocol. Emotional functioning is particularly affected, while cognitive function remains somewhat preserved. Phlebitis, observed in 64% of participants, necessitates active management during treatment. Fatigue emerges as a distressing symptom regardless of disease stage, with financial implications exacerbating patient challenges. Adherence to FOLFOX therapy is moderately observed (54%), highlighting the need to address symptoms and concerns to enhance patient outcomes and treatment adherence.

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Conflicts of interest
There are no conflicts of interest.

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