

# Evaluation of Adjuvant Short CAPOX Followed by Capecitabine for Stage III Colon Cancer

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## ABSTRACT

**Background:** Since 2004, 6 months of postsurgical adjuvant chemotherapy with combination of 5-FU/LV or oral Capecitabine and Oxaliplatin has been the standard of care worldwide for patients with stage III colon cancer. Objectives: to evaluate the efficacy of 3-months of Capecitabine and Oxaliplatin (CAPOX) followed by 3 months Capecitabine alone as adjuvant treatment in stage III colon cancer.

**Methods:** This is a prospective study that included 50 patients with stage III colon cancer who presented to National Cancer Institute, Cairo University to receive adjuvant CAPOX for three months followed by three months Capecitabine alone where disease free survival (DFS) & overall survival (OS) and toxicity were evaluated.

**Results:** The median age of patients was 43 years (range: 21-70) with male predominance. The majority of patients (70%) had right-sided lesions and N1 stage (64%). After a median follow up period of 36.8 months (range: 9.5-50.8); the 3-year cumulative DFS & OS were 57.2 & 86.3% respectively. Patients' age, presence of comorbidity, higher grade, development of chemotherapy-related peripheral neuropathy (PN), N2 stage, perineural invasion (PNI) and lymph node ratio (LNR) > 0.25 were significantly associated with worse DFS whereas, the latter two were significantly related to worse OS. Diarrhea, vomiting, hand-foot syndrome and PN were the most common grade 3 toxicities. The latter was significantly higher in patients with preexisting diabetes.

**Conclusion:** This small phase II study suggests that shorter duration of adjuvant oxaliplatin in stage III colon cancer might be associated with less toxicity especially peripheral neuropathy but still shows comparable survival to the six-months regimen. Further larger scale prospective randomized trial is mandatory to confirm these results.

**Key words:** colon cancer, stage III, adjuvant, CAPOX, neurotoxicity

## INTRODUCTION

Colorectal cancer is the second- and third-most common cancer in women and men, respectively. In 2012, 614,000 women (9.2% of all new cancer cases) and 746,000 men (10.0% of new cancer cases) were diagnosed with colorectal cancer worldwide. Combined, in both sexes, colorectal cancer is the third-most common cancer and accounts for 9.7% of all cancers excluding non-melanoma

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skin cancer (1). In Egypt, according to the results of the National Population-Based Cancer Registry Program, colon cancer is the 7<sup>th</sup> most common cancer as it constitutes 2.63% of all cancer cases (2).

For patients with stage III (lymph node-positive) colon cancer, 6 months of postsurgical adjuvant chemotherapy with leucovorin modulated 5-fluorouracil (5-FU/LV) was the standard of care from 1990 to 2004 based on clinical trials that demonstrated a 25% relative reduction in mortality over surgery alone (3).

Since 2004, the combination of 5-FU/LV or oral Capecitabine and Oxaliplatin became the standard of care worldwide based on the findings from three large trials; the MOSAIC trial, (NSABP) C-07 trial, and the NO16968 study (4).

The important question was how many cycles of Oxaliplatin should be administered with the objective of reducing treatment duration, toxicity, and cost of adjuvant therapy in colon cancer (4).

More recent data, support the plausibility of shorter duration treatment without loss of efficacy. Two studies, the MOSAIC and NSABP C-07, provided evidence in support of changing to shorter-duration FOLFOX doublet-based treatment (4).

Consequently, independent trials worldwide are currently in progress to gather data and perform a prospective combined analysis to answer the single primary hypothesis that 3 months of adjuvant therapy with Oxaliplatin-based chemotherapy is non-inferior to the current standard of six months for patients with stage III colon cancer (4).

The aim of this study is to evaluate the efficacy and safety of 3-months (4 cycles) of Capecitabine and Oxaliplatin (CAPOX) followed by 3 months (4 cycles) Capecitabine alone as adjuvant treatment in stage III colon cancer. The primary end point is DFS at 2 years and secondary end points are OS, safety and toxicity.

## PATIENTS AND METHODS

This is a prospective study that included 50 patients with stage III colon cancer who presented to National Cancer Institute, Cairo University for their adjuvant treatment. Patients received CAPOX for three months followed by three months Capecitabine alone.

Eligibility criteria: potentially curative surgical resection of pathologically proven stage III colon adenocarcinoma (any TN1/2M0), age  $\geq 18$  years, Eastern Cooperative Oncology Group performance score of  $\leq 2$ , No previous chemotherapy, normal blood counts, liver and kidney functions, pregnant or lactating patients and those with history of other malignancies were excluded.

Treatment protocol: three months CAPOX followed by three months Capecitabine. Oxaliplatin 130 mg/m<sup>2</sup> IV infusion over two hours (day 1 every three weeks) in combination with Capecitabine administered orally at a dose of 1000 mg/m<sup>2</sup> twice-daily for two weeks and one week off, followed by oral Capecitabine in the same dose for 3 more months. Chemotherapy related toxicities were assessed after each cycle of chemotherapy treatment and were graded based on NCI-CTCAE, V 4.0. Oral dose modification in response to adverse events and toxicity was conducted on the basis of standard clinical practice.

## Statistical analysis

Statistical analysis was done using IBM SPSS® Statistics version 22 (IBM® Corp., Armonk, NY, USA). Numerical data were expressed as mean and standard deviation or median and range as appropriate, while qualitative data were expressed as frequency and percentage. Survival analysis was done using Kaplan-Meier method and comparison between two survival curves was done using log-rank test. All tests were two-tailed. A p-value  $< 0.05$  was considered significant. OS was calculated from the date of enrolment in the study until the date of death or lost follow up. DFS was calculated from the date of curative surgical resection until the date of relapse, death or lost follow up.

## RESULTS

The mean age of the studied group was  $46.5 \pm 14.1$  years, ranging between 21 and 70 years, while the median was 43 years with male predominance (60%). Sixteen percent of the patients presented with complications in the form of obstruction and bleeding per rectum. Right side affection was predominant (70%). Preoperative serum CEA and CA 19.9 were measured in 19 patients. CEA was high in 2 patients (10.5%), while CA 19.9 was normal in all patients. Postoperative serum CEA and CA 19.9 was normal in all patients.

Clinicopathological characteristics of 50 cases of restricted stage III colon cancer was shown in *tables 1, 2*.

Adenocarcinoma being the main pathological type (52%) followed by mucinous adenocarcinoma (36%). Grade 2 disease was more common than grade 3 and T-stage at diagnosis was T3 in 80% of cases. The median number of total lymph nodes removed during surgery was 20 (range: 8-41). The majority of patients (92%) had  $\geq 12$  nodes removed. Positive nodes were  $> 3$  in 18 patients (36%). Median lymph node ratio (defined as number of positive lymph nodes/the number

**Table 1 - Clinical characteristics of 50 case of restricted stage III colon cancer**

| Clinical Parameter             | No. | %    |
|--------------------------------|-----|------|
| Age                            |     |      |
| < 40 yrs                       | 18  | 36.0 |
| ≥ 40 yrs                       | 32  | 64.0 |
| Sex                            |     |      |
| Male                           | 30  | 60.0 |
| Female                         | 20  | 40.0 |
| Associated comorbidities       |     |      |
| Diabetes Mellitus (DM)         | 12  | 24.0 |
| Hypertension                   | 6   | 12.0 |
| Hypertension + DM              | 2   | 4.0  |
| Family history of colon cancer |     |      |
| Positive                       | 10  | 20.0 |
| Negative                       | 40  | 80.0 |
| First presentation             |     |      |
| Pain                           | 21  | 42.0 |
| Intestinal Obstruction         | 3   | 6.0  |
| Bleeding per rectum            | 5   | 10.0 |
| Diarrhea                       | 3   | 6.0  |
| Mass                           | 1   | 2.0  |
| Constipation                   | 1   | 2.0  |
| Anemia + Pain                  | 1   | 2.0  |
| Performance state              |     |      |
| PS0                            | 3   | 6.0  |
| PS1                            | 44  | 88.0 |
| PS2                            | 3   | 6.0  |
| Anatomical site                |     |      |
| Cecum                          | 10  | 20.0 |
| Ascending Colon                | 22  | 44.0 |
| Transverse Colon               | 3   | 6.0  |
| Descending Colon               | 7   | 14.0 |
| Sigmoid Colon                  | 8   | 16.0 |
| Baseline serum tumor markers   | 19  |      |
| CEA                            |     |      |
| Normal                         | 17  | 89.5 |
| High                           | 2   | 10.5 |
| CA19.9                         |     |      |
| Normal                         | 19  | 100  |
| High                           | 0   | 0    |

Abbreviations: CEA: carcinoembryonic antigen, CA19.9: cancer antigen 19.9, PS: performance state.

**Table 2 - Pathological characteristics of 50 case of restricted stage III colon cancer**

| Pathological Parameter     | No. | %    |
|----------------------------|-----|------|
| Number of lesions          |     |      |
| Solitary                   | 47  | 94.0 |
| Multiple                   | 3   | 6.0  |
| Pathological types         |     |      |
| Adenocarcinoma             | 28  | 56.0 |
| Mucinous adenocarcinoma    | 18  | 36.0 |
| Adenocarcinoma Signet Ring | 3   | 6.0  |
| Undifferentiated carcinoma | 1   | 2.0  |
| Grade                      |     |      |
| Grade 2                    | 39  | 78.0 |
| Grade 3                    | 11  | 22.0 |
| T Stage                    |     |      |
| T2                         | 5   | 10.0 |
| T3                         | 40  | 80.0 |
| T4                         | 5   | 10.0 |
| N Stage                    |     |      |
| N1                         | 32  | 64.0 |
| N2                         | 18  | 36.0 |
| Lymphovascular involvement | 40  |      |
| No                         | 21  | 52.5 |
| Yes                        | 19  | 47.5 |
| Perineural involvement     | 40  |      |
| No                         | 35  | 87.5 |
| Yes                        | 5   | 12.5 |
| LN capsular involvement    | 41  |      |
| No                         | 35  | 85.4 |
| Yes                        | 6   | 14.6 |
| Number of removed LN       |     |      |
| < 12                       | 4   | 8.0  |
| ≥ 12                       | 46  | 92.0 |
| LN Ratio                   |     |      |
| ≤ 0.25                     | 34  | 68.0 |
| > 0.25                     | 16  | 32.0 |

Abbreviations: LN: lymph node, T Stage: primary tumor stage

of total lymph nodes) was 0.12 (range: 0.02-0.72) with a cutoff point of 0.25 used to correlate with DFS and OS.

Lymphovascular and perineural involvement was reported in 19 and 5 cases out of 40 known cases, respectively, while lymph node capsular involvement was reported in 6 out of 41 known cases (14.6%) as showing in *table 2*.

Three months CAPOX followed by three months Capecitabine was administered to 47 patients; as three patients decided to take standard treatment with 6 months CAPOX after enrollment in the study. Treatment adherence (i.e., the percentage of patients who received all planned therapy) was 95.7%.

The median follow up period of the studied group was 36.8 months (range: 9.5-50.8 months), while the cumulative DFS proportion at 36 months of the whole studied group was 57.2%. Patients' age (≥ 40) and presence of comorbidity were associated with a worse DFS ( $p = 0.015$ ,  $p = 0.002$ , respectively). *Table 3* shows

**Table 3 - DFS in relation to demographic and clinical prognostic factors**

|                                | n  | Events | DFS at 36 months | p value |
|--------------------------------|----|--------|------------------|---------|
| Whole Group                    | 47 | 18     | 57.2%            |         |
| Age                            |    |        |                  |         |
| < 40 yrs                       | 18 | 2      | 88.9%            | 0.015   |
| ≥ 40 yrs                       | 29 | 16     | 43.0%            |         |
| Sex                            |    |        |                  |         |
| male                           | 29 | 12     | 48.0%            | 0.495   |
| female                         | 18 | 6      | 65.8%            |         |
| Comorbidity                    |    |        |                  |         |
| no                             | 26 | 4      | 84.6%            | 0.002   |
| yes                            | 21 | 14     | 31.4%            |         |
| Family history of colon cancer |    |        |                  |         |
| negative                       | 37 | 14     | 57.2%            | 0.616   |
| positive                       | 10 | 4      | 60.0%            |         |
| PS                             |    |        |                  |         |
| PS0                            | 3  | 3      | 0.0%             | *       |
| PS1                            | 41 | 14     | 61.1%            |         |
| PS2                            | 3  | 1      | 66.7%            |         |

\* Statistically not applicable.

Abbreviations: PS: performance state.

**Table 4 - DFS in relation to tumor-related prognostic factors**

|                            | N=47 | Events | DFS at 36 months | p value |
|----------------------------|------|--------|------------------|---------|
| Site                       |      |        |                  |         |
| Right                      | 34   | 12     | 57.1%            | 0.478   |
| Left                       | 13   | 6      | 53.8%            |         |
| Lesion size                |      |        |                  |         |
| < 7 cm                     | 17   | 6      | 64.7%            | 0.648   |
| ≥ 7 cm                     | 30   | 12     | 57.9%            |         |
| Pathology                  |      |        |                  |         |
| Adenocarcinoma             | 28   | 13     | 50.9%            | 0.198   |
| Mucinous adenocarcinoma    | 18   | 4      | 77.4%            |         |
| Grade                      |      |        |                  |         |
| 2                          | 36   | 11     | 63.6%            | 0.011   |
| 3                          | 11   | 7      | 34.1%            |         |
| T Stage                    |      |        |                  |         |
| T2                         | 5    | 0      | 100.0%           | 0.375   |
| T3                         | 37   | 16     | 53.1%            |         |
| T4                         | 5    | 2      | 60.0%            |         |
| N Stage                    |      |        |                  |         |
| N1                         | 30   | 6      | 75.5%            | < 0.001 |
| N2                         | 17   | 12     | 27.5%            |         |
| Lymphovascular involvement |      |        |                  |         |
| No                         | 20   | 7      | 60.6%            | 0.843   |
| Yes                        | 17   | 6      | 64.7%            |         |
| Perineural involvement     |      |        |                  |         |
| No                         | 32   | 8      | 72.7%            | < 0.001 |
| Yes                        | 5    | 5      | 0.0%             |         |
| LN capsular invasion       |      |        |                  |         |
| No                         | 33   | 11     | 64.5%            | 0.056   |
| Yes                        | 5    | 4      | 0.0%             |         |
| LN ratio                   |      |        |                  |         |
| ≤ 0.25                     | 34   | 7      | 75.5%            | < 0.001 |
| > 0.25                     | 13   | 11     | 15.4%            |         |

DFS in relation to demographic and clinical prognostic factors.

DFS was significantly worsened by presence of more than 3 positive lymph nodes (nodal stage N2) ( $p < 0.001$ ), higher grade ( $p = 0.011$ ), perineural involvement ( $p < 0.001$ ) and a lymph node ratio  $> 0.25$  ( $p < 0.001$ ).

Table 4 shows DFS in relation to tumor-related prognostic factors.

The median OS was not reached by the end of the study while the overall cumulative survival proportion of the whole studied group was 86.3%. OS was not significantly affected by age ( $p = 0.851$ ), sex ( $p = 0.249$ ), comorbidity ( $p = 0.290$ ), family history ( $p = 0.067$ ), and performance status as shown in table 5.

Perineural involvement was associated with significantly worse OS ( $p = 0.001$ ) as well as a lymph node ratio  $> 0.25$  ( $p = 0.027$ ) as table 6.

## DISCUSSION

Since 2004, oxaliplatin with a fluoropyrimidine has been standard adjuvant chemotherapy in patients with

**Table 5 - OS in relation to demographic and clinical prognostic factors**

|                                | n  | Events | DFS at 36 months | p value |
|--------------------------------|----|--------|------------------|---------|
| Whole Group                    | 47 | 6      | 86.3%            |         |
| Age                            |    |        |                  |         |
| < 40 yrs                       | 18 | 2      | 88.9%            | 0.851   |
| ≥ 40 yrs                       | 29 | 4      | 85.0%            |         |
| Sex                            |    |        |                  |         |
| male                           | 29 | 5      | 81.2%            | 0.249   |
| female                         | 18 | 1      | 94.4%            |         |
| Comorbidity                    |    |        |                  |         |
| no                             | 26 | 2      | 92.3%            | 0.290   |
| yes                            | 21 | 4      | 79.7%            |         |
| Family history of colon cancer |    |        |                  |         |
| negative                       | 37 | 3      | 91.1%            | 0.067   |
| positive                       | 10 | 3      | 70.0%            |         |
| PS                             |    |        |                  |         |
| PS0                            | 3  | 1      | 66.7%            | *       |
| PS1                            | 41 | 4      | 89.4%            |         |
| PS2                            | 3  | 1      | 66.7%            |         |

Abbreviations: PS: performance state

**Table 6 - OS in relation to tumor-related prognostic factors**

|                            | N=47 | Events | DFS at 36 months | p value |
|----------------------------|------|--------|------------------|---------|
| Site                       |      |        |                  |         |
| Right                      | 34   | 4      | 86.6%            | 0.869   |
| Left                       | 13   | 2      | 84.6%            |         |
| Lesion size                |      |        |                  |         |
| < 7 cm                     | 17   | 3      | 82.4%            | 0.331   |
| ≥ 7 cm                     | 30   | 3      | 89.5%            |         |
| Pathology                  |      |        |                  |         |
| Adenocarcinoma             | 28   | 5      | 82.1%            | 0.275   |
| Mucinous adenocarcinoma.   | 18   | 1      | 90.0%            |         |
| Grade                      |      |        |                  |         |
| 2                          | 36   | 3      | 91.7%            | 0.105   |
| 3                          | 11   | 3      | 68.6%            |         |
| T Stage                    |      |        |                  |         |
| T2                         | 5    | 0      | 100.0%           | 0.404   |
| T3                         | 37   | 6      | 82.5%            |         |
| T4                         | 5    | 0      | 100.0%           |         |
| N Stage                    |      |        |                  |         |
| N1                         | 30   | 2      | 92.0%            | 0.109   |
| N2                         | 17   | 4      | 76.5%            |         |
| Lymphovascular involvement |      |        |                  |         |
| No                         | 20   | 2      | 88.8%            | 0.484   |
| Yes                        | 17   | 3      | 82.4%            |         |
| Perineural involvement     |      |        |                  |         |
| No                         | 32   | 2      | 92.6%            | 0.001   |
| Yes                        | 5    | 3      | 40.0%            |         |
| LN capsular invasion       |      |        |                  |         |
| No                         | 33   | 4      | 86.8%            | 0.519   |
| Yes                        | 5    | 1      | 80.0%            |         |
| LN ratio                   |      |        |                  |         |
| ≤ 0.25                     | 34   | 2      | 92.8%            | 0.027   |
| > 0.25                     | 13   | 4      | 69.2%            |         |

Abbreviations: LN: lymph node, T Stage: primary tumor stage, N stage: lymph node stage

stage III and high-risk stage II colon cancer. Three phase 3 trials convincingly showed that the addition of oxaliplatin improved DFS; with longer follow-up, these findings were extended to overall survival (5).

Accordingly, a 6-month regimen of FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPOX (Capecitabine and Oxaliplatin) became the standard adjuvant therapy in stage III disease (6).

The risk of oxaliplatin-based sensory neurotoxicity depends on the cumulatively administered dose of the drug. Neurotoxicity often peaks several months after the last oxaliplatin exposure, which makes empirical dose individualization difficult. Such toxic effects can be severe and persist long beyond the actual treatment, which potentially affects patients' activities of daily living for the rest of their lives (6).

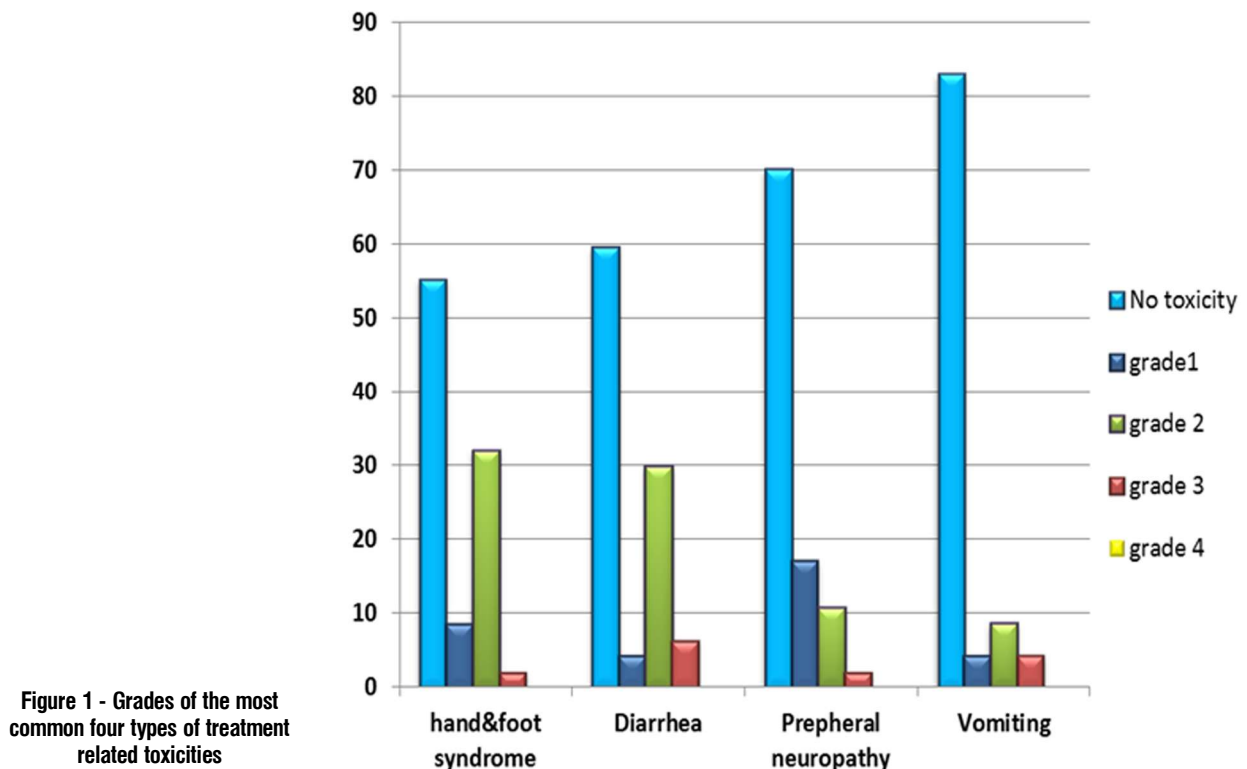
Therefore, this prospective study was designed to evaluate the efficacy and safety of 3-months (4 cycles) of CAPOX followed by 3 months (4 cycles) Capecitabine alone as adjuvant treatment in stage III colon cancer. This regimen was evaluated for its effect on delaying or preventing recurrences, its impact on both DFS and OS as well as evaluation of its toxicity. The study included 50 patients with stage III colon cancer who were treated at NCI, Cairo University. Their age ranged from 21 to 70 years with a mean of  $46.5 \pm 14.1$  years. An important remark in the current series is that, patients

40 years or younger constituted thirty-six percent of the studied group with male predominance. However, it is consistent with age distribution in previous published hospital-based studies from Egypt which report that more than one third of colorectal cases are younger than 40 (7) (8).

Population based studies also have shown high CRC rates at young age. Ibrahim et al., reported that the average age is 50 years old in Egypt. While another population-based study showed that the incidence rate of CRC for those less than 40 years of age in Egypt was 22.0% of all cases, which is higher than the United States incidence rate for the same age group with male to female ratio of 1.2:1 (2) (9).

Family history criteria and pathologic features of tumors in young Egyptian patients do not differ significantly from those in older patients implying that they are likely to have a similar etiology. Hereditary risk factors are unlikely the cause associated with this unusual pattern of early-onset CRC in Egyptian patients (10).

The increase in colon cancer in younger patients has been previously reported. Siegel et al., demonstrated an increased incidence of CRC in men and women under the age of 50 at a rate of 2.1 percent per year from 1992 through 2012 with incidence and mortality rates of 30% and 40% higher in men than in women, respectively (11).



Reasons for higher rates in men are not completely understood, but to some extent likely reflect differences in exposures to risk factors and sex hormones, as well as complex interactions between these influences (12).

All patients presented with different grades of symptoms before curative treatment. The most common clinical presentation of the studied group was pain (42%), followed by intestinal obstruction (36%).

Three of our patients (6%) had history of previous appendectomy. Although studies have rarely investigated whether appendicitis truly increases the cancer risk, and its mechanism a follow-up study using large Asian population data showed that patients with appendicitis are at an elevated risk of colorectal cancer after appendectomy. The overall risk elevation is estimated to be 14%, but is much greater in elderly patients (13).

On the other hand, in a Swedish trial, no excess gastrointestinal cancer risks were observed among patients with previous appendectomy, with the possible exception of esophageal cancer (14).

The most common site of cancer was the ascending colon (44%), followed by cecum (20%). Collectively, 35 patients (70%) had right sided lesions (RCC) and 15 (30%) had left sided lesions (LCC). There was no significant survival difference between both sides in the current study which may be due to the small number of patients recruited.

Currently, data on the prognosis for patients with nonmetastatic RCC and LCC are conflicting, and whether the tumor's location itself has a significant prognostic impact remains a matter for debate (15).

Previous studies have also reported that patients with stage III RCC likely present a significantly increased mortality risk compared with those with LCC. By analyzing various stages of colorectal cancer, Huang et al., observed a poorer OS in patients with RCC than those with LCC, whereas significant differences were only noted in stage III patients (16).

For patients treated with curative resection and subsequent oxaliplatin-based adjuvant chemotherapy, Sinicrope et al., found that RCC was significantly associated with a shorter DFS than LCC in patients with BRAF wild type stage III colon cancer (17). Similarly, Zhang et al., demonstrated that both the 5-year recurrence-free survival and 5-year OS were significantly different; survival gradually decreased for caecal tumors till the sigmoid tumors (18).

However, how many adjuvant chemotherapy cycles were administered was not discussed in the above-mentioned studies. In a retrospective study, Peng et al., demonstrated that tumors arising on different sides generate different prognostic outcomes in patients with

stage III colon cancer who received adjuvant chemotherapy after curative resection. The full course of adjuvant chemotherapy might only benefit RCC patients. However, the underlying mechanisms creating different outcomes after a full course of adjuvant chemotherapy for RCC and LCC remain unclear. They considered that advanced tumors were more frequently observed on the right side, and these tumors might benefit from more intensive chemotherapy (19). Although most studies showed poorer survival for primary tumors located on the right side, a study by Weiss et al., demonstrated no difference between the 5-year OS for patients with RCC and LCC after adjusting for multiple variables; instead, they found that the mortality in patients with stage II RCC was lower than it was in those with LCC (20). A population-based Surveillance, Epidemiology, and End Results (SEER) analysis of patients with nonmetastatic colon cancer provided evidence that the prognosis for patients with RCC was better regarding OS and cancer-specific survival (CSS). Subgroup analyses of patients with stages III colon cancer showed that the prognosis for RCC and LCC patients was similar (15).

Until now, heterogeneity within the literature, including the study designs, disease stages, and treatment information, has been significant. Additional research is required to define the factors and tumor biology more clearly with regard to colon cancer laterality (15).

In the current study, adenocarcinoma was the main pathological type of colon cancers (56%), followed by mucinous adenocarcinoma (36%) with signet ring carcinoma comprising (6%) while undifferentiated carcinoma (2%). Pathological grade II was identified in (78%) of cases while (22%) were grade III.

This is consistent with Foda et al, study showing excess mucinous carcinoma among Egyptians, especially signet ring variant in comparison with the world rates (8).

The majority of our patients (92%) had  $\geq 12$  nodes excised during surgery and  $> 3$  positive nodes were identified in 18 patients (36%). Lymphovascular involvement was reported in 19 out of 40 known cases (47.5%) and it was associated with worse DFS ( $P < .0001$ ) but not with OS.

Perineural involvement was reported in 5 out of 40 known cases (12.5%) while, Lymph node capsular involvement reported in 6 out of 41 known cases (14.6%).

The lymph node ratio defined as number of positive lymph nodes / the number of total lymph nodes evaluated in our study revealed that a cutoff point of

0.25 was significantly affecting both DFS ( $P < .0001$ ) and OS ( $p = 0.027$ ).

Lymph node ratio independently predicts prognosis in stage III colon cancer and may thus act as a confounder. Previous reports of

The prognostic significance of total number of lymph nodes in node-positive colon cancer were confounded by lymph nodes ratio. The 12-node standard for total number of lymph nodes may not be equally applicable in right-sided and left-sided colon cancer. SEER database of 63,243 stage III patients with colon cancer were identified by Yang et al, who reported that after adjusting for lymph nodes ratio, the association of the total number of lymph nodes with survival in stage III colon cancer was present only in right-sided colon cancer but not in left-sided colon cancer (21).

In the current study, the median follow up period of the studied group was 36.8 months. The cumulative DFS proportion at 36 months of the whole studied group was 57.2%. Patients' age and presence of comorbidity were associated by worse DFS ( $p = 0.015$ ,  $p = 0.002$ , respectively).

DFS was significantly worsened by presence of more than 3 positive lymph nodes ( $p < 0.001$ ), higher grade ( $p = 0.011$ ), nodal stage N2 ( $p = 0.001$ ), and perineural involvement ( $p < 0.001$ ). Also, patients who develop chemotherapy-related peripheral neuropathy had worse DFS ( $p = 0.005$ ) While it is not affected by Sex, positive family history nor treatment-related prognostic factors.

In the current study at 36 months the cumulative OS proportion of the studied group was 86.3%. Perineural involvement was associated with significantly worse OS ( $p = 0.001$ ) also, longer time period between diagnosis and surgery was associated with better OS ( $p = 0.001$ ) which may reflect indolent disease. On the other hand, time from surgery to chemotherapy and duration of chemotherapy did not affect overall survival.

OS was not significantly affected by age, sex, comorbidity, family history or performance status. Otherwise, the remaining tumor-related factors or toxicity-related prognostic factors did not affect OS.

Survival outcomes in our study were compared with trials that examined CAPOX as adjuvant treatment in stage III colon cancer for 6 months. CAPOX in adjuvant colon cancer treatment (XELOXA) trial investigated the addition of oxaliplatin to an oral fluoropyrimidine in the adjuvant treatment of colon cancer. CAPOX was compared with bolus FU/FA in patients with stage III colon cancer. The median number of chemotherapy cycles received was 8.0 (range, 1 to 9) in the CAPOX group (22).

The 3-year DFS rate was 70.9% with CAPOX being superior to the bolus FU/FA (66.5%) with a HR of 0.80 (95% CI, 0.69 to 0.93;  $P .0045$ ). The hazard ratio for OS for CAPOX compared to FU/FA was 0.87 (95% CI, 0.72 to 1.05;  $P .1486$ ). The 5-year OS for CAPOX and FU/FA were 77.6% and 74.2%, respectively (22).

The 3-year DFS rates in both arms of XELOXA trial is better than DFS in our study which is suggested to be due to differences in clinicopathological criteria between studied groups. The median age for patients in XELOXA trial was 61 years old in the CAPOX arm and 62 years old in the bolus FU/FA arm. In our studied cohort, the median age was 43 years old. Thirty-six percent of the studied cohort was below 40 years of age. More mucinous adenocarcinoma were reported in the current study (36%) compared with that in the XELOXA trial (22). Forty six percent of patients in our study presented with complications in the form of intestinal obstruction (36%) and rectal bleeding (10%).

Another randomized phase III trial of FOLFOX versus CAPOX as adjuvant chemotherapy in patients with early-stage colorectal adenocarcinoma conducted by Pectasides was conducted. It randomized 201 patients to FOLFOX and another 213 to CAPOX for 6 months. Three-year DFS was 79.8% (95% CI 76.5-83.4) in the FOLFOX group and 79.5% (95% CI 75.9-83.1) in the CAPOX group ( $p=0.78$ ). Three-year OS was 87.2% (95% CI 84.1-91.1) and 86.9% (95% CI 83.4-89.9) in the in FOLFOX and CAPOX groups respectively (23).

Inclusion of stage II in that trial explains high DFS in comparison to our trial, SCOT was a randomized, phase III noninferiority trial conducted in several European countries conducted on 6,088 patients with high-risk stage II/III colon cancer. Patients were randomized to receive either 3 or 6 months of adjuvant CAPOX or FOLFOX (24).

SCOT is significant in that it enrolled the largest number of patients treated with CAPOX. The results showed that a 3-months adjuvant chemotherapy was noninferior to 6-months therapy in patients with stage III colon cancer, with the same 3-year DFS rate in both groups (HR, 1.015; 95% CI, 0.909-1.132). A post-hoc analysis of 3-year DFS for patients in the CAPOX group revealed that 3 months of CAPOX therapy was significantly noninferior to 6 months of therapy. The 3-year DFS was 76.9% in the 3-months therapy group vs 76.1% in the 6-months therapy group (HR, 0.944; 95% CI, 0.835-1.067;  $P$  [for noninferiority] = .002). While, 3 years OS was 90% for 3 months group and 89.6 for 6 months group (24).

ACHIEVE was another phase III trial conducted in Japan that randomized patients with stage III colon

cancer to receive either 3 or 6 months of mFOLFOX6 or CAPOX adjuvant chemotherapy. A total of 1,313 patients were randomized (15% T1/T2, 57% T3, 28% T4, and 26% N2) (25).

The 3-year DFS rate in ACHIEVE trial was 79.5% in the 3-months group and 77.9% in the 6-months group (HR, 0.954; 95% CI, 0.758-1.201). Subgroup analysis revealed that the HR was 0.811 (95% CI, 0.532-1.236) in patients with low-risk features (T1-T3 and N1) and 1.066 (95% CI, 0.810-1.403) in patients with high-risk features (T4 or N2). HR was 1.065 (95% CI, 0.709-1.600) in patients treated with FOLFOX and 0.904 (95% CI, 0.684-1.195) in those treated with CAPOX (25).

Hand and foot syndrome was the most common encountered treatment toxicity in the current study, (44.6%), followed by diarrhea (40.4%) and peripheral neuropathy (30%).

In general grade 2 or 3 toxicity occurred in 35 patients (72.9%), while 13 patients (27.1%) had grade 1 toxicity and 7 patients had Grade 3 toxicity (14.7%). None of our patients had grade 4 toxicity of any type.

The most common grade III toxicity was diarrhea (6.3%), followed by vomiting (4.2%), peripheral neuropathy (2.1%) and Hand-foot syndrome (2.1%). Our study reports neutropenia to be presented in (2.1%) which was better than that seen in Pectasides study where the most common grade 3-4 toxicities were neutropenia (13.8% with FOLFOX vs 4.4% with CAPOX,  $p < 0.0001$ ) and Vomiting was more frequent in the CAPOX group (1.6% vs 0%,  $p = 0.017$ ) (23).

The primary safety concern with the use of oxaliplatin is peripheral neuropathy, a cumulative dose-related toxicity. In this study, peripheral neuropathy grade 1 occurred in (17%) of cases, while (10.6%) and (2.1%) had grade 2 and 3 respectively.

Treatment related peripheral neurotoxicity was significantly higher in association with comorbidity ( $p = 0.018$ ). There was no relation between age, comorbidity, or timing of treatment with grade 2 or 3 of other toxicity types.

These findings are consistent with the results from Pectasides et al, where sensory neuropathy was reported to be (3.2% with FOLFOX vs 2.1% with CAPOX,  $p = 0.25$ ). While, in XELOXA trial grade 3/4 neurosensory toxicity was evident in 11% of CAPOX - treated patients for 6 months (22).

In the IDEA trial the shorter duration of adjuvant therapy was associated with significantly lower rates of adverse events than a longer duration, independent of the chemotherapy regimen. Peripheral neurotoxicity of grade 2 or higher during active therapy and in the month after cessation of treatment was substantially

lower in the 3-months therapy group (16.6% with FOLFOX and 14.2% with CAPOX) than in the 6-months therapy group (47.7% with FOLFOX and 44.9% with CAPOX). In addition, rates of diarrhea, neutropenia, thrombocytopenia, nausea, mucositis, fatigue, and the hand-foot syndrome were also substantially lower with shorter treatment duration (26).

In SCOT, the frequency of grade  $\geq 3$  toxicities was significantly higher in the 6-months than in the 3-months group (59% vs 36%;  $P < .0001$ ): diarrhea (17% vs 12%;  $P = .033$ ), neutropenia (14% vs 10%;  $P = .031$ ), pain (6% vs 2%;  $P = .014$ ), and hand-foot syndrome (5% vs 2%;  $P = .031$ ). Peripheral neuropathy of grade 2 or worse was more common in the 6 months group (58%) than in the 3 months group (25%) and was long-lasting associated with worse quality of life (24).

While, in ACHIEVE trial, the frequency of grade  $\geq 2$  neurotoxicity was significantly lower in the 3-months therapy group than in the 6-months group (14% vs 36%;  $P < .001$ ) (25).

Peripheral neuropathy of more than grade 2 in our study was 12.7% which is consistent with 3-months therapy group in ACHIEVE trial and less than shown in SCOT trial.

The findings reported here should be viewed with the limitations of the single arm with small sample size of the study and also clinicpathological differences of colon cancer in Egypt.

## CONCLUSION

This preliminary small sized phase II clinical study using adjuvant (CAPOX) following curative surgical treatment for stage III colon cancer patients had shown less toxicity by reducing the dose of Oxaliplatin to only three months especially peripheral neurotoxicity with still comparable survival to the six months regimen.

The cumulative DFS proportion at 36 months of the whole studied group was 57.2% while OS was 86.3%.

Special patient's characteristics were found to affect the result of treatment as patient's age and presence of comorbidity which were associated by worse DFS. In addition, DFS was significantly worsened by lymph node ratio of more than 0.25, higher grade, nodal stage N2, perineural involvement and developing chemotherapy - related peripheral neuropathy.

Perineural involvement and lymph node ratio of more than 0.25 was associated with significantly worse OS. Larger prospective randomized comparative study is required to evaluate the non-inferiority of 3 months CAPOX followed by Capecitabine than 6 months CAPOX for stage III colon cancer. Also, to assess the safety and



cost effectiveness in view of recent recommendations for patient's classification in order to personalize treatment decisions which offers great opportunity for selecting the right therapies for our patients in the future.

### *Conflict of interest*

All author declare that they have no conflict of interest.

### *Ethics of approval*

The study was approved of the Ethical Committee in National Cancer Institute.

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