

## Phase II trial: perioperative chemotherapy with surgical resection in initially respectable prognostically unfavorable colorectal liver metastases

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**Abstract: Background:** For patient with resectable colorectal liver metastases (CRLM) with adverse prognostic features, upfront surgery or neoadjuvant chemotherapy represent two treatment approaches which require more randomized trials to enable the treating team to select the most appropriate one to start with. The objective of our study was to assess the clinical outcome of perioperative chemotherapy with surgical resection in this kind of CRLM.

**Methods:** 36 patients with respectable CRLM and unfavorable prognostic features were assigned to receive perioperative 8 cycles of XELOX (capecitabine and oxaliplatin) regimen with resection of liver disease. Patient evaluation included assessment of clinical response, disease free survival, and overall survival along with toxicity.

**Results:** The preoperative chemotherapy resulted in overall response rate (complete response and partial response) of 44.5% (16/36), and tumor control rate (overall response and stable disease) of 86.1% (31/36) whereas complete response was observed in only one patient (2.8%). The median survival for all patients was 34 months and 3 years OS was 46% while the median survival for respected patients not reached, 3 years OS was 57.5% and 3 years DFS was 41.3%. Neutropenia was the most common hematologic toxicity, recorded in 4 patients (11.1%). No mortality due to hematologic toxicity was recorded. Most of the non-hematological toxicities were mild and manageable.

Sensory neuropathy was the most common treatment-related adverse event, occurring in 66.6% (24/36) of patients.

**Conclusions:** The current study suggests that perioperative XELOX regimen is an active and safe chemotherapy regimen for this kind of initially resectable CRLM with poor prognostic features.

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**Keywords:** perioperative chemotherapy; surgical resection; colorectal liver metastases

### 1. Introduction:

The optimal treatment strategies for colorectal liver metastases (CRLM) are evolving rapidly with improved clinical outcomes being achieved when the treatment options are evaluated within a multidisciplinary team to review CRLM cases [1,2]. The treatment strategy should be aimed towards complete resection whenever possible, taking both ‘oncological’ (prognostic) and ‘technical’ (surgical) criteria in consideration when evaluating patients for surgery [3].

The ‘technical’ definitions of resectable CRLM have evolved over time, with current consensus proposing that disease should be considered technically resectable as long as complete macroscopic resection is feasible, while maintaining at least a 30% future liver remnant (FLR) or a remnant liver to body weight ratio >0.5%. The ‘oncological’ criteria provide prognostic information that predicts a longer disease-free survival (DFS) or a higher likelihood of cure [4,5]. Fong and Nordlinger risk parameters for recurrence after hepatic resection included age, number of lesions, size of the largest lesion, the disease-free interval from the primary to the discovery of the liver metastases, T status of the primary, the nodal status of the primary, and

preoperative CEA level [6,7]. Thus, for some patients, neoadjuvant chemotherapy may be required and represents a better option than upfront surgery.

This randomized phase II trial was conducted to assess the clinical outcome of perioperative chemotherapy with surgical resection in initially resectable but with unfavorable prognostic features CRLM.

### 2. Patients and Methods:

#### Patient Selection

Between January 2013 and March 2016, 36 patients over the age of 18 years with CRLM were subjected to this phase II study, at Clinical Oncology Department, and Surgery Department, Faculty of Medicine, Tanta University Hospital. All patients had liver metastases diagnosed radiologically and confirmed histopathologically in questionable cases.

Eligible patients were required to have initially resectable liver metastases, judged by the surgical oncology team with the aid of a diagnostic radiologist when needed, with three or more unfavorable prognostic features defined by Fong and Nordlinger risk parameters which included: age > 60 years, disease-free interval < 24 months, number of lesions >1, size of the largest lesion ≥ 5 cm, T status of the

primary  $\geq$  T3, positive nodal involvement of the primary, and CEA level  $>$  200 ng/ml. Inclusion criteria included, age ranged between 18 and 70 years; Karnofsky performance status (KPS) of  $\geq$  70; adequate bone marrow reserve (WBC count  $\geq$  3.5  $\times$  10<sup>9</sup>/L, ANC count  $\geq$  1.5  $\times$  10<sup>9</sup>/L, platelets  $\geq$  100  $\times$  10<sup>9</sup>/L, and hemoglobin  $\geq$  10 g/dL), adequate renal function (measured creatinine clearance  $\geq$  60 mL/min) and adequate liver function (transaminases less than 2  $\times$  upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Patients with earlier chemotherapy for treatment of the metastatic disease, prior adjuvant or neoadjuvant chemotherapy with capecitabine and/or oxaliplatin, malabsorption disease, lack of physical integrity of the upper GI tract, history of severe neuropathy, ventricular arrhythmia, congestive heart failure or documented myocardial infarction, signs or symptoms of extrahepatic metastasis, second malignant disease, pregnant or lactating mothers and any other uncontrolled medical illness were considered ineligible.

All patients provided written informed consent prior to enrolment into the study. The Ethics Committee at our Faculty of Medicine, Tanta University granted protocol approval.

#### Patient Evaluation before Entering the Study

All patients had a complete medical history and physical examination before entering the study. Furthermore, baseline blood tests included complete blood count, CEA measurement, and liver and renal function tests. Radiological assessment involved liver imaging with ultrasound, computed tomography (CT), and/or magnetic resonance imaging(MRI), and chest radiographs.

#### Treatment

The primary tumor had to be technically resectable but with at least three unfavorable prognostic features as judged by the medical oncology and surgical oncology team at Clinical Oncology Department, and Surgery Department, Faculty of Medicine, Tanta University Hospital.

We chose the XELOX (capecitabine and oxaliplatin) regimen for the study since capecitabine has been combined successfully with oxaliplatin in a variety of different schedules to produce an effective and viable treatment option in both the first and second-line settings for patients with metastatic colorectal cancer (MCRC) [8].

Patients were assigned to receive 8 cycles of XELOX regimen, four cycles over three months before and four cycles over three months after surgery unless disease progression or unacceptable toxicity occurred.

Eligible patients received a 120-minute intravenous infusion of oxaliplatin 130 mg/m<sup>2</sup> on day 1

(diluted in a 5% dextrose solution) plus oral capecitabine 1000 mg/m<sup>2</sup> twice daily from day 1 night to day 15 morning of a 3-week cycle administered on an outpatient basis.

Before oxaliplatin infusion, hydration, adequate anti-emetic therapy, antacids and steroids were ensured for all patients. Growth factor (G-CSF) and antibiotic were administered in some cases, based upon clinical judgment. Adequate hematological and organ functions recovery should be ensured before each treatment session. Dose reduction was allowed according to clinical judgment. Patients with treatment delay of more than 3 weeks were withdrawn from the study.

Surgery of metastases (liver resection) was allowed 3–5 weeks after the last administration of preoperative chemotherapy, and whenever patients had completely recovered from chemotherapy toxicity with KPS of  $\geq$  70; adequate bone marrow reserve (WBC count  $\geq$  3.5  $\times$  10<sup>9</sup>/L, ANC count  $\geq$  1.5  $\times$  10<sup>9</sup>/L, platelets  $\geq$  100  $\times$  10<sup>9</sup>/L, and hemoglobin  $\geq$  10 g/dL), adequate renal function (measured creatinine clearance  $\geq$  60 mL/min) and adequate liver function (transaminases less than 2  $\times$  upper normal limit, and serum bilirubin concentrations below 1.5 mg/dL).

Intraoperative ultrasonography was used to detect and localize all hepatic metastases. The type and extent of curative liver resection were decided by the surgical oncology team at the time of randomization but was modified if previously undetected deposits were discovered, or if the tumor size was larger than was expected.

#### Patient Assessment

##### *Assessment of Clinical Benefit, Follow-up and restaging*

During the preoperative part of treatment, Pre- and on-treatment monitoring consisted of medical history, physical and neurological examination, abdomen and pelvis ultrasound, CT-scan of the chest, abdomen and pelvis, and CEA measurement. Tumor response assessment was performed after every two cycles of treatment and tumor response was determined according to the Response Evaluation Criteria in Solid Tumors, RECIST criteria [9], with the overall response rate, included complete response and partial response, while, the disease control rate, included complete response, partial response and stable disease.

Following surgery and during the postoperative part of treatment, patients were monitored carefully for the adverse reactions of treatment. Also abdomino-pelvic CT and/or MRI, and tumor marker after every two cycles of treatment were performed for detection of any recurrence.

After completion of treatment, patients were evaluated by physical examination, chest radiography,

and abdomino-pelvic CT every 3–4 months for detection of any disease recurrence. Biopsy was rarely performed from new recurrent sites of the disease.

#### **Assessment of Toxicity**

Patients were evaluated using a directed history, physical and neurological examination biweekly during treatment. Furthermore, a complete blood count and liver and renal function tests were conducted before every cycle during treatment. The occurrence and nature of any adverse events were recorded. Toxicity grading was based on the common terminology criteria for adverse event (NCI-CTC, version 4.0) [10].

#### **Study Endpoint**

The primary endpoint of this study was the disease free survival and the secondary end point was overall survival.

#### **Statistical analysis:**

The date of final analysis was May 2017. Disease-free survival was calculated according to the Kaplan-Meier method [11] with SPSS [Statistical package] (version 21.0). Mean and standard deviation were estimates of quantitative data. The 95% confidence intervals (95% CIs) were calculated with the exact method. Statistical significance was assessed by the log-rank test. All *P* values were two-tailed; a value of 0.05 was considered significant.

### **3. Results:**

#### **Patients Characteristics**

A total of 36 patients were enrolled in this phase II trial from January 2013 to March 2016 at Clinical Oncology Department, and Surgery Department, Faculty of Medicine, Tanta University Hospital.

The characteristics of all eligible patients are listed in Table 1. The median age of study participants was 61 years (range, 35–70 years), 66.7% (24/36) of patients were male. The primary tumor sites were: colon, 21 patients (58.3%); rectum, 12 patients (33.3%); and both colon and rectum, 3 patients (8.3%). The majority of patients received previous chemotherapy 52.8% (19/36) which consisted of intravenous 5-fluorouracil, with or without a bio-modulating agent.

At time of study entry, the median KPS was 80%, and more than half of the patients 55.6% (20/36) had a KPS of ≤ 80%. Median time between primary diagnosis of colorectal cancer to inclusion was 22 months (range 4–50 months). Most of the patients 55.6% (20/36) had multiple liver metastases. Only 8 patients (22.2%) had liver metastasis that ≥ 5 cm. Most of the patients 80.6% (29/36) had metachronous liver metastases. Most cases of liver metastases 72.2% (26/36) diagnosed within 24 months from the primary tumor (Table 1).

#### **Treatment**

**Table 1. Patient Characteristics (N = 36)**

| Patient Characteristics  | No. | %     |
|--|-----|-------|
| <b>Sex</b>   |     |       |
| Male   | 24  | 66.70 |
| Female   | 12  | 33.30 |
| <b>Age, years</b>  |     |       |
| Median   |     | 61    |
| Range  |     | 35-70 |
| <b>Karnofsky performance status%</b>   |     |       |
| 70   | 6   | 16.67 |
| 80   | 14  | 38.89 |
| 90   | 11  | 30.56 |
| 100  | 5   | 13.89 |
| <b>Type of cancer</b>  |     |       |
| Colon only   | 21  | 58.30 |
| Rectal only  | 12  | 33.30 |
| Colon and rectal   | 3   | 08.30 |
| <b>T category of the primary cancer</b>  |     |       |
| T1   | 1   | 02.80 |
| T2   | 13  | 36.10 |
| T3   | 16  | 44.4  |
| T4   | 6   | 16.70 |
| <b>Nodal status of the primary cancer</b>                                      |     |       |
| N0   | 18  | 50.00 |
| N1   | 12  | 33.30 |
| N2   | 6   | 16.60 |
| <b>Time from diagnosis of primary to diagnosis of liver metastases (years)</b> |     |       |
| <2   | 26  | 72.20 |
| ≥2   | 10  | 27.80 |
| <b>Number of liver metastasis</b>  |     |       |
| Single metastasis  | 16  | 44.40 |
| Multiple metastases  | 20  | 55.60 |
| <b>Size of largest liver metastasis</b>  |     |       |
| <5 cm  | 28  | 77.70 |
| ≥5 cm  | 8   | 22.20 |
| <b>Synchronicity of liver metastases</b>                                       |     |       |
| Metachronous metastases  | 29  | 80.60 |
| Synchronous metastases   | 7   | 19.40 |
| <b>CEA level</b>   |     |       |
| <200 ng/ml   | 26  | 72.20 |
| ≥200 ng/ml   | 10  | 27.70 |
| <b>Previous adjuvant chemotherapy for primary cancer</b>                       |     |       |
| No   | 17  | 47.20 |
| Yes  | 19  | 52.80 |

Patients were assigned to receive pre-and postoperative chemotherapy, four cycles of XELOX over three months each part unless disease progression or unacceptable toxicity occurred.

A total of 264 cycles of XELOX were given. The median number of XELOX cycles was 7 (range 2–8).

All cycles were initiated at the initially planned doses. A total of 28 patients (77.7%) completed all the planned preoperative and postoperative 8 cycles. One patient (2.7%) received only 3 cycles preoperatively and could not receive the fourth one because of toxicity but we added it to the postoperative part of treatment. Two patients (5.5%) completed the four preoperative cycles but received only 3 cycles postoperatively because of unacceptable toxicity. Five patients (13.8%) received all or part of the preoperative treatment and progressed and could not undergo resection (the progression was evident after 2 cycles in one patient and discontinued treatment, while it needed 4 cycles to become clear in the other four patients) and did not receive the planned XELOX cycles but had been shifted to 5-fluorouracil, leucovorin, and irinotecan regimen (FOLFIRI).

Surgery of metastases (liver resection) was allowed 3–5 weeks (median 4 weeks) after the last administration of preoperative chemotherapy after complete recovery from chemotherapy toxicity with KPS of  $\geq 70$ ; adequate bone marrow reserve, and adequate renal and liver functions.

Intra-operative ultrasonography was of great help in detecting and localizing all hepatic metastases. All operated patients achieved R0 resection defined by the postoperative pathological report.

Five patients could not undergo resection due to disease progression, four patients developed new lesions and in the fifth one, his tumor size increased in size. After re-evaluation of those patients, all of them became ineligible for resection.

#### Response to preoperative Treatment

The primary goal of monitoring patients in the preoperative treatment part was to detect exactly the tumor response. The response to the preoperative part of the treatment was assessed after every two cycles of XELOX and illustrated in table 2. Overall response rate (complete response and partial response) was 44.5% (16/36), and tumor control rate (overall response and stable disease) was 86.1% (31/36) according to the RECIST criteria. Complete response was observed in only one patient (2.8%). All objective responses were confirmed at least 4 weeks after first observation.

Karnofsky performance status did not significantly affect response rates ( $P=0.202$ ). Response rate was significantly higher in patients with primary colonic carcinoma ( $P=0.001$ ), female patients ( $P<0.0001$ ), patients with solitary liver metastasis ( $P=0.001$ ), liver metastasis  $<5$  cm ( $P=0.045$ ), N-0 of the primary ( $P=0.009$ ), T-1T-2 primary ( $P=0.001$ ), time interval to metastases  $\geq 2$  years ( $P=0.011$ ), CEA level  $<200$  ng/ml ( $P=0.011$ ), patients with histopathological grade I/II tumors ( $P=0.004$ ), and in patients who had not received previous chemotherapy ( $P=0.021$ ) (Table 3).

**Table 2. Tumor Response to Preoperative Treatment**

| Tumor Response      | No. | %    |
|---------------------|-----|------|
| Complete response   | 1   | 2.8  |
| Partial response    | 15  | 41.7 |
| Stable disease      | 15  | 41.7 |
| Progressive disease | 5   | 13.9 |

**Table 3. Correlation between variables and tumor Response to preoperative Treatment**

| Variable                        | Overall response rate |                 | Total<br>No (%) | P-value  |
|---------------------------------|-----------------------|-----------------|-----------------|----------|
|                                 | CR-PR<br>No (%)       | SD-PD<br>No (%) |                 |          |
| <b>Gender</b>                   |                       |                 |                 |          |
| Female                          | 11 (30.6%)            | 1 (2.8%)        | 12 (33.3%)      |          |
| Male                            | 5 (13.9%)             | 19 (52%)        | 24 (67.7%)      | < 0.0001 |
| <b>KPS%</b>                     |                       |                 |                 |          |
| 90-100                          | 9 (25.0%)             | 7 (19.4%)       | 16 (44.4%)      |          |
| 70-80                           | 7 (19.4%)             | 13 (36.1%)      | 20 (55.6%)      | 0.202    |
| <b>Type of cancer</b>           |                       |                 |                 |          |
| Colon                           | 14 (38.9%)            | 7 (19.4%)       | 21 (58.3%)      |          |
| Rectal & Colorectal             | 2 (5.6%)              | 13 (36.1%)      | 15 (41.7%)      | 0.002    |
| <b>T stage</b>                  |                       |                 |                 |          |
| 1-2                             | 11 (30.6%)            | 3 (8.3%)        | 14 (38.9%)      |          |
| 3-4                             | 5 (13.9%)             | 17 (47.2%)      | 22 (61.1%)      | 0.001    |
| <b>N stage</b>                  |                       |                 |                 |          |
| 0                               | 12 (33.3%)            | 6 (16.7%)       | 18 (50.0%)      |          |
| 1-2                             | 4 (11.1%)             | 14 (38.9%)      | 18 (50.0%)      | 0.009    |
| <b>Histo-pathological grade</b> |                       |                 |                 |          |
| I-II                            | 14 (38.9%)            | 8 (22.2%)       | 22 (61.1%)      |          |
| III-IV                          | 2 (5.6%)              | 12 (33.3%)      | 14 (38.9%)      | 0.004    |

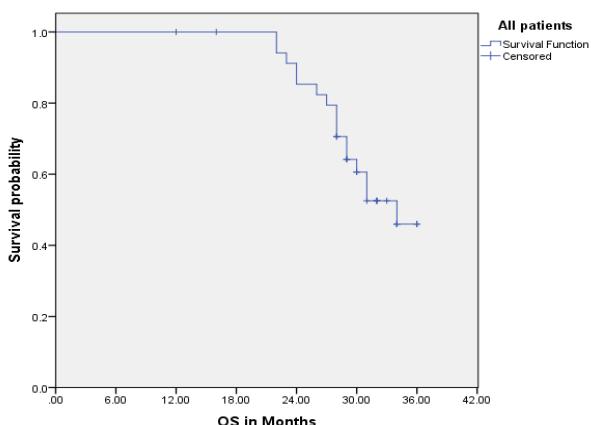
| Variable                                | Overall response rate |            | Total<br>No (%) | P-value |
|---|-----------------------|------------|-----------------|---------|
|   | No (%)                | CR-PR      | SD-PD           |         |
| <b>Number of liver metastasis</b>       |                       |            |                 |         |
| Single                                  | 12 (33.3%)            | 4 (11.1%)  | 16 (44.4%)      | 0.001   |
| Multiple                                | 4 (11.1%)             | 16 (44.4%) | 20 (55.6%)      |         |
| <b>Size of largest liver metastasis</b> |                       |            |                 |         |
| <5 cm                                   | 15 (41.7%)            | 13 (36.1%) | 28 (77.8%)      | 0.045   |
| ≥5 cm                                   | 1 (2.8%)              | 7 (19.4%)  | 8 (22.2%)       |         |
| <b>Time interval to metastasis</b>      |                       |            |                 |         |
| ≥ 2 years                               | 8 (22.2%)             | 2 (5.6%)   | 10 (27.8%)      | 0.011   |
| < 2 years                               | 8 (22.2%)             | 18 (50.0%) | 26 (72.2%)      |         |
| <b>CEA level</b>                        |                       |            |                 |         |
| < 200ng/ml                              | 15 (41.7%)            | 11 (30.6%) | 26 (72.2%)      | 0.011   |
| ≥200ng/ml                               | 1 (2.8%)              | 9 (25.0%)  | 10 (27.8%)      |         |
| <b>Previous adjuvant chemotherapy</b>   |                       |            |                 |         |
| No                                      | 11 (30.6%)            | 6 (16.7%)  | 17 (47.2%)      | 0.021   |
| Yes                                     | 5 (13.9%)             | 14 (38.9%) | 19 (52.8%)      |         |

**CR:** Complete response, **PR:** Partial response, **SD:** Stable disease, **PD:** Progressive disease, **KPS:** Karnofsky performance status

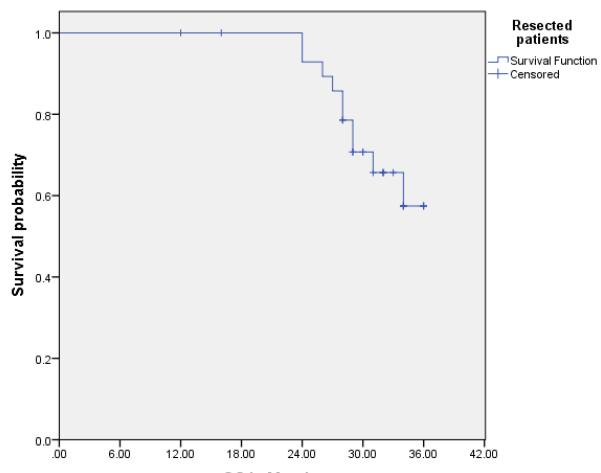
## Survival

Following surgical resection and the postoperative part of XELOX treatment, the patients were followed up regularly on definitive interval aiming at detection of any recurrence as early as possible for exact reporting the DFS and the possibility for the implication of another line of treatment hopefully for achieving a better survival.

For all patients, the median survival was 34 months and 3 years OS was 46% as shown in figure (1). For resected patients, the median survival couldn't be reached, and the 3 years OS and 3 years DFS were 57.5% and 41.3% respectively as shown in figure (2 & 3).



**Figure (1) The 3 –year Overall survival for all patients**



**Figure (2) The 3 –year Overall survival for resected patients**

## Toxicity

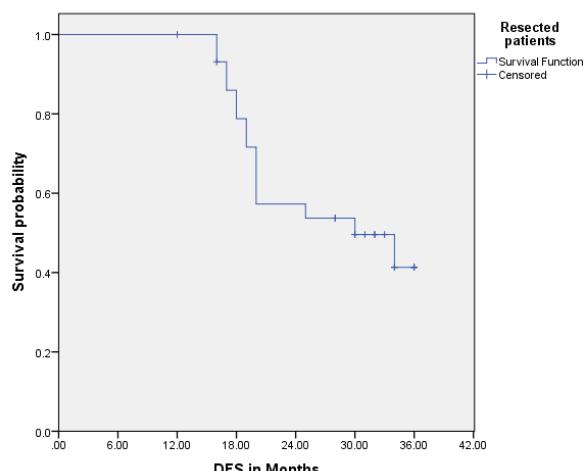
The major Grade 3/4 adverse reactions to this regimen are listed in Table 4. Neutropenia was the most common Grade 3–4 hematologic toxicity, recorded in 4 patients (11.1%). No mortality due to Grade 3-4 hematologic toxicity was recorded.

Most non-hematological toxicities were mild and manageable. Sensory neuropathy was the most common treatment-related adverse event, occurring in 66.6% (24/36) of patients. The majority of neuropathy was mild to moderate. Grade 3/4 sensory neuropathy occurred in 8 (22.2%) patients. Hand-foot syndrome was experienced by 19 patients (52.8%) with only 4 patients (11.1%) suffered from grade 3. Other frequent grade 3 or 4 non-hematologic toxicities observed were

diarrhea in 7 patients (19.4%), nausea/vomiting in 6 patients (16.6%), and mucositis in 2 patients (5.6%).

A total of 8 patients required hospitalization for different reasons; deterioration in performance status (PS) in 2 patients, neutropenic fever in 1, bleeding in 1, infection in 1, anemia in 2, and severe mucositis in 1 patient.

32 patients (88.8%) received full doses of capecitabine and oxaliplatin throughout the preoperative period while only 23 patients (63.8%) did that during the postoperative part of treatment. Five patients received no more than two-four cycles due to rapid disease progression and could not undergo resection and received no further planned chemotherapy. A dose reduction was performed in 4 patients (11.1%) preoperatively and in 8 patients (22.2%) postoperatively with 25% reduction for both drugs. The dose reductions were decided all because of neutropenia and neurotoxicity.



**Figure (3) The 3-year Disease free survival for resected patients**

**Table 4. Grade 3/4 treatment-related hematologic and non-hematologic toxicity among all patients (N= 36 patients)**

| Treatment toxicity              | No. | %    |
|---------------------------------|-----|------|
| <b>Non-hematologic Toxicity</b> |     |      |
| Sensory neuropathy              | 8   | 22.8 |
| Diarrhea                        | 7   | 19.4 |
| Nausea/vomiting                 | 6   | 16.6 |
| Hand-foot syndrome              | 4   | 11.1 |
| Mucositis                       | 2   | 5.6  |
| <b>Hematologic Toxicity</b>     |     |      |
| Neutropenia                     | 4   | 11.1 |
| Anemia                          | 2   | 5.6  |
| Thrombocytopenia                | 1   | 2.8  |

#### 4. Discussion:

In the past years several studies have emphasized the role of combination of chemotherapy and surgery to be used as the way for improving survival in patients with CRLM [12]. Resectability and various prognostic features could affect the treatment decision whether surgery or chemotherapy should be upfront. Some perioperative chemotherapy regimens comprising 5-fluorouracil (5-FU) plus leucovorin in combination with oxaliplatin (FOLFOX) or irinotecan, typically FOLFIRI have been reported to facilitate the resection of liver metastases [13,14]. Previous phase II trials reported activity of XELOX combination in patients with advanced or MCRC [8,15] which compare favorably with the other studies of FU/LV with or without oxaliplatin [16,17,18].

In the current study, we worked on resectable CRLM with unfavorable prognostic features that would have a poor outcome if treated with surgical resection alone. We chose the perioperative way of delivering the planned XELOX combination chemotherapy.

In the current study, the administration of preoperative XELOX combination in patients with CRLM was associated with a 44.5% overall response rate (16/36), and tumor control rate (overall response and stable disease) of 86.1% (31/36) according to the RECIST criteria. The Response rate was independent of baseline KPS. However, chemotherapy-naive patients, primary colonic carcinoma, female patients, patients who presented with solitary metastases, metastases < 5 cm, time interval to metastases  $\geq$  2 years, CEA < 200ng/ml, T1-2 status of the primary, N-0 status of the primary, and histo-pathological grade I/II tumors had higher response rates than others, even though the number of patients in this study was low. The median survival for all patients was 34 months and 3 years OS was 46% while for resected patients, the 3 years OS was 57.5% and 3 years DFS was 41.3%. These results were comparable with that reported by Nordlinger et al [19] who conducted a randomized trial comparing perioperative chemotherapy with hepatic resection versus surgery alone in CRLM. They demonstrated that in the perioperative chemotherapy group the objective response rate was 43% and disease stabilization was achieved in 38% of the patients. They reported a 3-year DFS of 42.4% in the perioperative chemotherapy group which was significantly better compared to that reported in surgery group, 33.2%.

Regarding this treatment approach, our study confirmed the overall acceptable tolerability and compatibility of perioperative chemotherapy with hepatic resection. The perioperative chemotherapy did not appreciably increase the incidence of hematologic

and non-hematologic toxicity. To date, most of the adverse reactions to this regimen observed in our 36 assessable patients were manageable. The frequency of the toxicity profile of this regimen was somewhat higher than previously reported in other studies using the XELOX/FOLFOX [19,20], probably because of a high percentage of relatively poor performance was presented in this study participants. More than half of the patients had a performance status of 80% or less. Many investigators demonstrated an increased risk of toxicities in patients with lower performance status when they were receiving chemotherapy [16]. Interestingly, previous reports showed that the incidence of grade 3 or 4 neutropenia is lower with the XELOX regimen than with the FOLFOX4 regimen (11.1% v 42% to 47%) [19,20]. In addition, XELOX regimen is easy to administer in an outpatient basis, therefore, this dose and schedule were considered appropriate for this population.

In conclusion, the current results suggest that perioperative XELOX regimen is an active and safe chemotherapy regimen for this kind of initially resectable with poor prognostic features CRLM. Because the tolerability, response rates, and DFS of the perioperative XELOX regimen was not inferior to previous studies of FU/LV/oxaliplatin, in addition, the XELOX combination is easy to administer in outpatients, this constitutes a marked advantage over regimens combining infused FU/LV and oxaliplatin [13,14] in terms of the impact on improving the level of treatment-related quality of life. However, we do not know whether the outcome would be better if we utilized a triplet instead of duplet chemotherapy or if we added anti-EGFR antibodies or Bevacizumab. Further prospective trials are required to figure out the optimum treatment combination and intensity aiming at increasing response with acceptable toxicities reflecting eventually on better survival. Another question which needs further prospective trials to be answered: is it safe to skip chemotherapy in prognostically favorable CRLM?

## 5. Compliance With Ethical Standards:

### Conflict of Interest

The author Esam A. Abo-Zenad declared that he has no conflict of interest. The author Mohamed F. Sheta declared that he has no conflict of interest.

### Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent:

Informed consent was obtained from all individual participants included in the study.

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