Prophylactic HIPEC in colon cancer patients with minimal serosal involvement: A pilot study

Khadiga Amr Abdel Kader¹, Sherif Ismail Maamoun¹, Osman Mohamed Mansour², Ihab Saad Hussein¹, Ghada Mohamed Abdelsalam³, Ahmed Mostafa Ahmed¹

¹Department of Surgical Oncology, National Cancer Institute, Cairo University, Egypt
²Department of Medical Oncology, National Cancer Institute, Cairo University, Egypt
³Department of Pathology, National Cancer Institute, Cairo University, Egypt

Corresponding author
Department of Surgical Oncology, National Cancer Institute, Cairo University, Egypt;
Email: Khadiga.ak@gmail.com

Citation

ABSTRACT

Background: In 10%-35% of patients with recurrent colorectal cancer tumor recurrence is confined to the peritoneal cavity, leading ultimately to death from complications of loco regional tumoral widespread. Aim: To determine the oncological effectiveness of prophylactic HIPEC in preventing the development of peritoneal carcinomatosis in colorectal cancer patients having minimal serosal involvement. Patients and methods: This is a randomized control pilot study on an eligible group of 21 colorectal cancer patients undergoing a curative colectomy. In which prophylactic HIPEC was administered in the experimental arm, or adjuvant systemic chemotherapy alone in the standard treatment arm. HIPEC was mitomycin based; it was a 90-minute session and was applied simultaneously. The effectiveness of prophylactic HIPEC was determined by the peritoneal-recurrence free survival among both groups at 18 months. Results: The median peritoneal-recurrence free survival for the experimental arm was 17 months, while in the standard treatment arm it was 12 months (p-value 0.250). There were no perioperative mortalities among both groups, and only one patient in the experimental arm developed a deep surgical site infection. Conclusion: Prophylactic HIPEC did not seem to have a major role in the prevention of peritoneal carcinomatosis in colorectal cancer. This statement cannot be made with certainty before a full-scale randomized control trial is conducted. In addition, to the higher incidence of nodal capsular infiltration among the experimental arm; this negatively impacts survival and conceals the benefit of HIPEC among the experimental arm.

Keywords: Colorectal cancer, Minimal serosal involvement, peritoneal carcinomatosis, Prophylactic HIPEC.
1. INTRODUCTION

The worldwide incidence rate of colorectal cancer reached 1.8 million cases/year and mortality rates reached 9.2% it is considered the third and second most common cancer in men and women respectively. Isolated peritoneal metastasis is reported in 10%-35% of patients with recurrent colorectal cancers. Those patients have been shown to ultimately die from complications of loco regional tumoral widespread, in most cases without occurrence of metastases in other sites (Coccolini et al., 2013). Situations that could result in a substantially higher risk of recurrent peritoneal carcinomatosis (PC) after curative surgery for colorectal cancer include: resected minimal synchronous macroscopic PC, synchronous isolated ovarian metastases, perforated primary tumour at initial surgery, positive peritoneal cytology, mucinous and signet ring histologies, serosal involvement and adjacent organ invasion (Honore et al., 2013).

Unlike the treatment of isolated liver metastases, the treatment of isolated peritoneal metastases is less established and remains controversial (Coccolini et al., 2013). Left untreated the biologically aggressive nature of PC impairs the functional status of patients to an extent that makes them eligible only for palliative, best supportive care only with an overall median survival of 5.0 months (Pelz et al., 2010). Peritoneal carcinomatosis from colorectal cancer (PCCRC) is assigned the worst disease stage (Stage IV C) according to the AJCC TNM staging, a highly morbid condition with no consensus on a standard treatment plan (Amin et al., 2017). This was the main drive to undergo this study, aiming at a proactive strategy to avoid the occurrence of carcinomatosis in those at risk.

2. PATIENTS AND METHODS

This study included 21 Colorectal Cancer (CRC) patients undergoing a curative colectomy at the National Cancer Institute (NCI), Cairo University (CU), between January 2017 and December 2018. Eligible patients were those diagnosed with adenocarcinoma of the colon and either one of the following high-risk features for the development of peritoneal carcinomatosis: a locally advanced primary tumour (T4N0-2M0), either consisting of obvious T4a where gross tumour was seen at the serosal surface of the colon intra-operatively, or T4b where there was adjacent organ infiltration. In addition to patients, they having minimal peritumoural peritoneal deposits resected at the same time as the primary. Female patients with ovarian metastases were also included.

All the 21 patients were randomised intra-operatively (in a 1:1 ratio) to prophylactic HIPEC, which was applied simultaneously following the colectomy and later followed by standard adjuvant systemic chemotherapy in the experimental arm, or adjuvant systemic chemotherapy alone in the standard treatment arm. Randomization was done using a random allocation sequence which was generated using random permuted blocks of 2 and a computerized random number table was used for sequence generation.

The effectiveness of prophylactic HIPEC was determined by the peritoneal-recurrence free survival among both groups at 18 months based on routine follow-up visits, CT imaging, CEA and CA19-9 as biochemical markers. Included patients were ages between 18 and 65 years, they had an adequate WHO performance status(< 2), the primary tumour was located in the colon or the upper rectum (above peritoneal reflection), and a written informed consent was signed by all patients. Application of HIPEC was performed simultaneously (same sitting as colectomy), over 90 minutes using the low-dose (40mg) Mitomycin C concentration-based regimen, the open “coliseum” technique was adopted, using 3 inflow cannulas (one used for manual irrigation of the exposed abdominal wall) and 2 outflow cannulas. The following were all excluded: appendiceal cancers, non-curable intent of treatment, liver and/or lung metastases, unstable or uncompensated respiratory or cardiac disease, and any major derangements of the routine pre-operative lab work.

Excel sheets were constructed to include the following data for all patients

- Patient demographics
- Preoperative imaging studies, colonoscopy and biopsy results
- Operative details, operative time and intraoperative complications
- Course of the postoperative hospital stay and the need for readmission shortly after discharge
- Final histopathological results including T stage, grade and adenocarcinoma subtype if present
- Course of the routine adjuvant systemic treatment including complications, treatment interruption and delays in starting treatment
- Routine follow up and monitoring for peritoneal recurrence by frequent history taking and physical examination, biochemical markers (CA19-9 and CEA) and CT imaging up to 18 months from the date of the surgical procedure. Peritoneal recurrence became evident by one or more of the following clinical events: abdominal pain, continuum of bowel obstruction manifestations, elevated markers and radiologically visible intra-abdominal deposits.

© 2020 Discovery Scientific Society. All Rights Reserved. www.discoveryjournals.org | OPEN ACCESS
Statistical analysis
This was a multivariate analysis. Data was analyzed using SPSS (Statistical Package of Social Sciences). Numerical data was described as mean and standard deviation or median and range, as appropriate. Categorical data was summarized by numbers and percentages. Comparisons between the two groups were performed by the chisquare test or the Fisher’s exact test, as appropriate. Survival estimates were calculated using the Kaplan-Meier method and the differences between the two groups were tested using the Logrank test. A p-value less than to 0.05 was considered statistically significant. All tests were two-sided tests. Peritoneal disease-free survival was calculated from surgery date till the date of documented recurrence or till the end of the 18-month follow up period.

3. RESULTS
Among the 21 study patients there were 15 (71.4%) females and 6 (28.6%) males and the mean age was 48 years. Their demographic data are listed below in table 1.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean± Standard deviation</td>
<td>48.0±12.5</td>
</tr>
<tr>
<td>Range</td>
<td>25-67</td>
</tr>
<tr>
<td>&lt; 50 years</td>
<td>13</td>
</tr>
<tr>
<td>≥ 50 years</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>15 (71.4%)</td>
</tr>
</tbody>
</table>

Pre-operative abdominal imaging indicated the presence of serosal involvement in all patients by one or more of the following radiological findings: bulky colonic mass infiltrating the surroundings in 10/21 patients (47.6%), colonic mural thickening with fat stranding in 14/21 patients (66.7%) or suspicious adnexal lesions in 4/15 female patients (19%). Illustration was shown in figure 1.

Figure 1 Radiological findings indicating the presence of serosal involvement

Laparoscopic exploration was performed in 3/21 of cases (14.3%) and an open laparotomy in 18/21 of cases (86%). Intraoperative findings were as follows in figure 2. Surgical resection was as follows in figure 3.

Additional resection was performed in 16/21 patients (76.2%). Resection was in the form of one or more of the following: Adjacent organ/ nearby structure resection in 8/16 patients (50%) in the form of a: partial cystectomy, small bowel resection, sleeve gastrectomy or resection of attached ventral or posterior abdominal wall musculature; Limited peritoneal resection in 4/16 patients (25%); Unilateral salpingoophrectomy or total abdominal hysterectomy and bilateral salpingoophrectomy where performed for female patients with suspicious adnexal lesions in 11/16 patients (68.7%).
Intra-operative findings indicating serosal involvement

This was followed by intra-operative (1:1) randomisation of the 21 study group patients, where 10 patients (47.6%) received simultaneous HIPEC while the remaining 11 patients (52.4%) were assigned to the no HIPEC arm. All the 10 patients in the HIPEC arm remained in the ICU for first 48 hrs for routine monitoring. One patient in the study group (4.8%), belonging to the experimental arm, developed a post-operative complication in the form of a deep surgical site infection. It was managed conservatively by percutaneous drainage and antibiotics. There were no post-operative mortalities. The median length of hospital stay was comparable among both groups (p-value 0.197), indicating that the addition of prophylactic HIPEC does not prolong the hospital stay when compared to standard treatment.

On final histopathological specimen assessment, 10 specimens (47.6%) were classified as T3 lesions with close radial margins, while the remaining 11 specimens (52.4%) were classified as T4a-T4b lesions. Regarding the nodal assessment 8 specimens (38.1%) were classified as having no nodal involvement, while another 8 specimens (38.1%) were staged as having N1 disease and the remaining 5 specimens (23.8%) were staged as having N2 disease. In patients where additional resection was performed (n=16 patients, 76.2%), histopathological infiltration was only confirmed in 10 of the 16 additional resection specimens (62.5%). All patients received adjuvant FOLFOX which commenced within 4 weeks from the date of the surgical procedure in 17 patients (81%) and in the remaining 4 patients (19%) beyond 4 weeks. Seventeen patients (81%) completed 6 months of adjuvant systemic treatment, while 4 patients (19%) had their treatment interrupted. Interruptions were due to treatment related toxicity in 2 patients (9.5%) and evident disease progression during treatment in the other 2 patients.

The median follow-up period for the whole study group was 16 months (ranged from 2 to 18 months), while the median peritoneal recurrence-free survival (PRFS) was 16 months and the cumulative PRFS at 12 months (1 year) was 52.4%, and at 18 months was 30.6%. The survival benefit of prophylactic HIPEC is demonstrated below, in figure 4, in which the median PRFS for the experimental arm was 17 months, while in the standard treatment arm it was 12 months. Cumulative PRFS at 18 months for the experimental arm was 50% and for the standard treatment arm was 12.1% (p-value 0.250).
The patients in both arms of the study group had comparable variables in terms of demographics, clinical presentation, pre-op work up results, operative details, primary tumor site, extent of resection, pathological T stage, pathological N stage, margin status, histological subtypes and timing of commencement and completion of adjuvant systemic treatment. The only variable that differed between both groups and was statically significant was the nodal capsular/ perinodal fat infiltration; it was higher among the experimental arm (80%) vs. the standard treatment arm (12.5%) (P-value 0.032). There were two variables that were strongly linked to the development of peritoneal recurrence, these were: rising post-operative tumour markers CEA and CA-19-9 and the extent of the nodal burden as illustrated in figures 5 and 6 respectively.

Figure 4 Peritoneal recurrence-free survival (months)

Figure 5 Post-operative rising tumour markers and it’s relation to peritoneal recurrence-free survival (months)

Figure 6 Nodal burden and it’s relation to peritoneal recurrence-free survival (months)
4. DISCUSSION

Although the results of our study on the benefit of prophylactic HIPEC in colon cancer patients at risk were not statistically significant (p-value 0.250); it did succeed in prolonging the duration of peritoneal recurrence-free survival with a median PRFS for the experimental arm of 17 months, and 12 months in the standard treatment arm. In addition to the fact, that there was a higher incidence of nodal capsular infiltration among the experimental arm which negatively impacts survival and conceals the benefit of HIPEC among the experimental arm. However, this variable is not amenable to standardization among treatment groups as this is a finding on the final pathology report which is not available at the time of randomization.

Regarding the results of the two largest RCTs trials in this field they have demonstrated no benefit from adjuvant HIPEC; in the PROPHYLCHIP trial (Goere et al., 2018) the primary end point was the 3-year disease free survival (DFS) reached 44% in the experimental group and 51% in the surveillance group did not differ (p=0.75) among both groups, while in the COLOPEC trial (Klaver et al., 2019) the primary end point was the 18-month peritoneal metastases free survival (PMFS) with no difference observed: 77% (control) versus 81% (experimental), HR 0.836 (0.489-1.428).

The results of the previously mentioned trials were not significant, which could have been due to a suboptimal study design in that they have used Oxaliplatin whose efficacy is currently in question as the chemotherapeutic agent during the HIPEC infusion, which has been described by Wim Ceelen as being the end of the road (Ceelen, 2019). They have also both delayed HIPEC administration to weeks and even months following the primary resection. In our study HIPEC is performed in the same sitting as the curative colectomy. The oncological benefits of performing simultaneous HIPEC as opposed to interval HIPEC is elucidated by an understanding of the pathophysiology of PC. The presence of the primary tumour with exfoliation of tumour cells during surgical manipulation is the first step in the pathophysiology of PC the so-called the peritoneal metastatic cascade. Another drawback of delaying adjuvant HIPEC to the postoperative period is the subsequent delay in the start of adjuvant systemic treatment. Results from a systemic review and meta-analysis of 10 studies involving more than 15,000 patients examined the effect of timing of adjuvant therapy after resection showed that each 4-week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant therapy should be administered as soon as the patient is medically able (Biagi et al., 2011). Finally, they have inconsistent patient selection criteria, where their high-risk populations were not accurately defined before proposing such invasive approaches that may place the patient in a worse condition, leading to morbidity or mortality (Sugarbaker, 2010). Selecting the high-risk patient before assigning him to an adjuvant treatment is of paramount importance. This led us to an initiative to define a scoring system to help predict the metachronous occurrence of PC as the sole location of tumour recurrence after potentially curative surgery for colon cancer: “Colon cancer and predictors of carcinomatosis: Risk stratification using the peritoneal recurrence score”. This Peritoneal recurrence score (PRS) is currently underway and will be used for patient selection when applying the full-scale RCT; it will be calculated based on a logistic regression model, with the occurrence of PC as the sole location of tumour recurrence being the dependent variable, and clinicopathologic variables as the covariates (such as T stage, adenocarcinoma subtype, sidedness, perforation, age, clinical presentation, peritumoral deposits, ovarian deposits, minimally resected PM).

Ending with the famous quote by Paul H. Sugarbaker on the hard cover of his most recently edited text book “Peritoneal metastases when optimally treated can be cured, in selected patients peritoneal metastases can be prevented” (Sugarbaker, 2017), patient selection using the previously mentioned scoring system once established is of utmost importance before attempting prevention. We have overcome those issues in our design by infusing Mitomycin instead of Oxaliplatin, performing the HIPEC procedure in the same sitting as the primary resection and including all the purported risk factors for developing carcinomatosis in our patient selection criteria. Given the magnitude of the morbidity and suffering those patients with peritoneal carcinomatosis of colorectal origin experience in addition to the financial burden it brings, we should not stop at the disappointing results of the two largest trials in this field; the COLOPEC and PROPHYLCHIP. In fact, we have discussed previously that their results might be attributed to a suboptimal study design.

5. CONCLUSION

To be able to make a reliable statement regarding the oncological effectiveness of adjuvant HIPEC we need to implement a full-scale RCT. We recommend applying this design over the appropriately calculated sample size (with 160 experimental subjects and 160 control subjects, over an accrual interval of 24 months, and additional follow-up after the accrual interval of 24 months). In addition, to the consideration of the Dutch (high-dose) mitomycin triple dosing regimen instead of the (low-dose) concentration-based regimen that we have used. We believe that if the study design is implemented as such, a much more reliable result regarding the oncological effectiveness of prophylactic HIPEC will be reached.
Abbreviations
CRC: colorectal cancer; HIPEC: hyperthermic intraperitoneal chemotherapy; PCCRC: peritoneal carcinomatosis of colorectal cancer; NCI,CU: national cancer institute, Cairo university; CRS: cytoreductive surgery; PRFS: peritoneal recurrence free survival; CT: computerised tomography; CEA: carcino-embryonic antigen; CA19-9: cancer antigen 19-9; RCT: randomised control trial; PC: peritoneal carcinomatosis; FOLFOX: folinic acid, fluorouracil, oxaliplatin; DFS: disease free survival; PMFS: peritoneal metastasis free survival; OS: overall survival; PRS: peritoneal recurrence score.

Acknowledgments
We would like to thank all those who helped us in the data collection and facilitated our process in the National Cancer Institute, Cairo University.

Financial resources
This study has not received any external funding.

Informed consent
Written and oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Conflict of interest
Authors declare that they have no conflicts of interest.

Ethical approval
This study was approved by our institutional cancer committee (Institutional Review Board, IRB #00004025).

Data and materials availability
All data associated with this study are present in the paper.

REFERENCES AND NOTES
8. Pelz JO, Chua TC, Esquivel J, Stojadinovic A, Doerfer J, Morris DL, Maeder U, Germer CT, Kerscher AG. Evaluation of best supportive care and systemic chemotherapy as treatment stratified according to the retrospective peritoneal surface
disease severity score (PSDSS) for peritoneal carcinomatosis of colorectal origin. BMC Cancer. 2010 Dec 22;10:689


Peer-review
External peer-review was done through double-blind method.

Article History
Received: 12 November 2020
Reviewed & Revised: 13/November/2020 to 15/December/2020
Accepted: 16 December 2020
E-publication: 23 December 2020
P-Publication: November - December 2020

Publication License
This work is licensed under a Creative Commons Attribution 4.0 International License.

General Note
We recommended authors to print article as color digital version in recycled paper. Discovery Scientific Society will not provide any prints for subscription.