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Pilot Study: Prophylatic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Colorectal Cancers at High Risk of Developing Peritoneal Metastases in a Tertiary Asian Centre

Chin Jin Seo[1,2]; Grace Hwei Ching Tan[1,2]*; Chin-Ann Johnny Ong[1-6]; Jolene Si Min Wong[1-4]; Nicholas Shannon[1,2]; Claramae Shulyn Chia[1-4]; Melissa Ching Ching Teo[1,2]

[1]Department of Sarcoma, Peritoneal and Rare Tumours, Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, 30 Hospital Boulevard 168583, Singapore.

[2]Department of Sarcoma, Peritoneal and Rare Tumours, Division of Surgery and Surgical Oncology, Singapore General Hospital, Outram Road 169608, Singapore.

[3]Sing Health Duke-NUS Oncology, Academic Clinical Program, Duke-NUS Medical School, 8 College Road 169857, Singapore.

[4]SingHealth Duke-NUS Surgery, Academic Clinical Program, Duke-NUS Medical School, 8 College Road 169857, Singapore.

[5]Division of Medical Sciences, Laboratory of Applied Human Genetics, National Cancer Centre Singapore, 30 Hospital Boulevard 168583, Singapore.

*[6]Institute of Molecular and Cell Biology, A*STAR Research Entities, 61 Biopolis Drive, Proteos 138673, Singapore.*

Abstract

Introduction: The second most common site of Colorectal Cancer (CRC) recurrence is the peritoneum. The primary aim of this study was to assess feasibility of prophylactic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Asian patients, and to determine the associated morbidity and time to start of adjuvant chemotherapy.

Materials and methods: Patients at high-risk of developing Peritoneal Metastases (PM) include the following: T4 on imaging, krukenburg tumours, perforated tumours, limited synchronous PM, and peritoneal fluid cytology positive for malignant cells. Recruited patients were divided into two groups; newly diagnosed CRC patients with any of the high-risk features (Group 1), and patients who had recent surgery (less than 8 weeks from recruitment) with histological confirmation of high-risk features (Group 2).

Results: 17 patients were recruited, of which there were 14 Group 1 patients and 3 Group 2 patients. Of the 14 patients in Group 1, 10 had T4 disease and another 4 had limited PM suspected on staging scans. All patients completed the cytoreductive surgery (CRS) and HIPEC procedure with no mortalities. 2 patients experienced major morbidity (Clavien Dindo sore 3 or 4). Median time to adjuvant chemotherapy was 42.5 days (IQR 34.5-51). Median length of stay (LOS) was 12.5 days (IQR 9-15) comparable to our control group (N=214), which included all patients undergoing CRS and HIPEC with a median LOS of 14 days (IQR 11-19, p=0.06).

Conclusion: Prophylactic HIPEC is feasible in a highly selected group of patients with newly diagnosed locally advanced CRC and those with limited synchronous PM, with appropriate time to receiving adjuvant chemotherapy.

Keywords: Prophylactic HIPEC; Peritoneal metastasis colorectal cancer; High risk colorectal cancer; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy.

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Correspondance: *Grace Hwei Ching Tan, Department of Sarcoma, Peritoneal and Rare Tumours, Division of Surgery and Surgical Oncology, National Cancer Centre Singapore, 30 Hospital Boulevard 168583, Singapore. Email: grace.tan@thesurgicaloncologyclinic.sg*

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Introduction

Colorectal Cancer (CRC) recurrence affects 30-40% of patients [1,2], with the second most common site of recurrence (25-35%) in the peritoneum [3]. In the past two decades, treatment of CRC with Peritoneal Metastases (PM) has changed dramatically with the invention of Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy (CRS and HIPEC). This mode of treatment has improved the survival rates in this group of patients from 6 months if no treatment was given [4], to 5-year survival rates of 40-45% [5]. Some are even considered cured with 5-year survival rates of up to 16% [6].

Effectiveness of CRS and HIPEC depends largely on the extent of peritoneal disease which is typically described by the Peritoneal Cancer Index (PCI) score, and the Completeness of Cytoreduction (CC) score [7]. The role of CRS and HIPEC in established advanced CRC with PM has been studied extensively. Recently, studies where HIPEC is given in the prophylactic setting in patients at high-risk of developing PM have shown promising results, improving Disease-Free Interval (DFI) and Overall Survival (OS) (median overall survival 59.5 vs 52 months) [8]. However, there have also been two recent multicentre randomised controlled trials, which did not show an improved DFI in high-risk patients undergoing prophylactic CRS and HIPEC. In the COLOPEC trial, HIPEC was given 5-8 weeks after the initial surgical resection [9]. With the PROPHYLOCHIP PRODIGE 15 trial, systematic relook laparotomy and HIPEC were performed after having received 6 months of adjuvant chemotherapy [10]. Hence, we wanted to assess the role of prophylactic HIPEC in improving DFI and OS in our group of Asian patients.

Our primary aim was to test the feasibility of performing prophylactic HIPEC for CRC patients at high-risk of developing peritoneal recurrence in our institution, and determine the morbidity associated with such a procedure. The secondary aim was to determine the effectiveness of prophylactic HIPEC in preventing the development of PM in patients with CRC at high-risk of peritoneal recurrence.

Material and methods

Study design and participants

This is a pilot study performed at the National Cancer Centre Singapore and Singapore General Hospital. The trial is registered under ClinicalTrials.gov (Identifier: NCT03422432), and approved by Sing Health (CIRB No. 2017/2402/B) and the Health Sciences Authorities.

Patients were categorized into the following 2 groups:

Group 1: Patients diagnosed preoperatively with CRC and high-risk features of developing PM based on staging scans.

Group 2: Patients who have undergone initial surgery and found to have high-risk features of developing PM.

We hypothesized that the following features increases the risk of developing PM [11]:

1. T4 tumours-in Group 1, this would consist of obvious clinical T4 stage based on preoperative imaging, and in Group 2, this would be on pathological confirmation of a T4 tumour.

2. Krukenburg tumours-Unilateral or bilateral ovarian masses seen on preoperative imaging.

3. Perforated tumours-in Group 1, this would consist of patients presenting with perforation on preoperative imaging, and undergoing curative resection, and in Group 2, this would be on pathological or intra-operative confirmation of a perforated tumour.

4. Limited synchronous PM (peritoneal nodules <1 cm in the omentum and/or close to the tumour). Patients with limited peritoneal disease in close proximity to the primary tumour, that may be removed en bloc with the primary resection can be included, but patients with more extensive peritoneal disease and those with extra-peritoneal metastases i.e., liver and/or lung metastases will be excluded from the study.

5. Positive cytology in Group 2 patients

The other inclusion and exclusion criteria were as follows:

Inclusion criteria

- Patients must be between the ages of 21 and 75 years.
- Patients must be in a stable clinical condition to undergo simultaneous HIPEC after the primary curative colorectal resection.
- Patients must have an ECOG performance status 0 or 1
- Patients must have normal organ and marrow function as defined below:

Absolute neutrophil count	>1.5x10^9/L
Platelets	>100x10^9/L
Haemoglobin	>9.0 g/dl
Total bilirubin	≤1.5xULN
AST (SGOT)/ALT (SGPT)	<3 x institutional upper limit of normal (ULN)
Creatinine	≤1.5 x (ULN) or
Creatinine clearance	≥60 mL/min for patients with
Creatinine levels	>1.5 x institutional UL

- Patients must have a normal coagulation profile.
- Patients must give written informed consent.

Exclusion criteria

- Patients who are not fit to give consent for the procedure.
- Patients who are not fit to undergo surgery.
- Patients who are pregnant.
- Patients who have extensive synchronous peritoneal disease.
- Patients with extra-peritoneal metastases i.e., liver and/or lung metastases.

Patient recruitment

Patients were identified following consultation at our centre. All patients' clinical history, staging scans and histological report were discussed at the weekly multidisciplinary tumour board consisting of surgical oncologists, medical oncologists, radiation oncologists and radiologists, to reach a consensus on treatment plan. Once identified to fall within study criteria, patients were approached for informed consent for HIPEC. A total of 12 patients would be eligible for this procedure to be covered under the clinical trial.

Procedures and follow up

Eligible patients underwent surgery and prophylactic HIPEC at the Operating Theatre at a satellite site - Singapore General Hospital.

All surgeries were performed starting with an exploratory laparotomy. For those in Group 1, the procedure began with an exploration and resection of the primary tumour that was still in situ. Following which, any high-risk features were resected-limited peritoneal metastasis or krukenberg tumours. Patients in Group 2 underwent exploration followed by resection of any visible high-risk features prior to HIPEC.

In our centre, we use the closed abdomen HIPEC technique. Peritoneal perfusion is achieved by a closed circuit with inflow and outflow catheters placed through the skin. The laparotomy incision is closed with a running suture at the skin level to create a watertight seal. Crystalloid solutions are infused through the inflow catheter until a circuit is established within the abdominal cavity. We then use the Belmont hyperthermia pump to deliver the intra-peritoneal chemotherapy agent via a single inflow catheter and a heat exchanger. Once good flow is established, Mitomycin C (MMC) that is diluted in 2-2.5 L of peritoneal dialysate solution is supplemented to the perfusate and allowed to circulate in the cavity for 60 minutes. For this study, MMC was used for all HIPEC, given at a dose of 10 mg/Body Surface Area (BSA). The perfusate temperature is titrated to achieve an outflow temperature of 42^{o}C. At the end of the HIPEC procedure, the perfusion circuit is subsequently drained, the skin reopened and the abdomen inspected and lavaged with normal saline. The abdomen is then closed in standard fashion and the procedure concluded.

Follow-up was carried out at 3 monthly intervals during the first 12 months, then 6 monthly thereafter. All patients underwent CT scans of the chest, abdomen and pelvis at 6 monthly intervals to detect recurrence. Adverse events, procedures and other therapies administered were documented as well.

Patients who develop recurrent disease during the follow up period will be treated accordingly.

All relevant data during work up, management and follow up will be collected in an electronic case record form.

Control group

The control group was taken from a retrospectively collected database of 214 consecutive patients undergoing CRS and HIPEC from April 2001 to February 2016. All patients were included regardless of the primary tumour, PCI score, and chemotherapy agent used.

The aim was to compare the overall Length of Stay (LOS) and Clavien-Dindo (CD) scores between these 2 groups.

Statistical analysis

Results are presented as median (INTERQUARTILE RANGE (IQR)) for quantitative variables, based on the distribution of the data. When comparing this studies data to our control cohort, univariate analysis using Mann-Whitney U test was applied to obtain the p values.

Results

A total of 17 patients were recruited into this study from 1st September 2017 to 31st May 2021. Their ages ranged from 47-77 years of age. 10 patients were male and 7 were female.

14 out of 17 patients fell into Group 1. Of the 14 patients, 10 patients had T4 disease detected on preoperative scan and 4 patients had scan detected peritoneal disease. Of these, one patient with newly detected T4 disease had actually been treated for a colon cancer and underwent an extended right hemicolectomy 12 years prior to this, whereas another patient had previous subtotal colectomy 4 years prior to this for descending colon cancer and was now detected with local anastomotic recurrence and peritoneal limited disease on his surveillance scans.

Only 3 patients were in Group 2 – one had a perforated appendiceal tumour which required emergency appendicectomy, whereas the other 2 had limited peritoneal disease noted at index surgery. HIPEC was performed no later than 8 weeks after the index surgery.

All patients completed CRS and HIPEC with MMC. Postoperatively, median time to clear feeds (CF), full feeds (FF) and diet were 2 (IQR 2-2.) days, 4 (IQR 3-5) days and 6.5 (IQR 5-9) days, respectively. We used the CD scoring system to assess postoperative morbidity.12 of the patients scored 0. 2 patients had severe morbidity with a CD score of 3 and 4, whereas the other 2 patients had minor morbidity with CD score of 1 and 2. Of the patients who had severe morbidity, one had an anastomotic leak requiring relook laparotomy and hartmanns procedure. Another patient developed hospital acquired pneumonia postoperatively, necessitating the patient to be admitted into the surgical intensive care unit (SICU) for further management. These 2 patients eventually recovered and were discharged home well.

Median LOS was 12.5 (IQR 9-15) days, and median time to adjuvant chemotherapy was 42.5 (IQR 34.5-51) days. Only 11 patients eventually went on to receive adjuvant chemotherapy. For the remaining 6 patients, two were low-risk stage II on the final histology, and the other four patients had declined adjuvant chemotherapy.

On follow up, 6 patients were subsequently detected to have recurrence. Site of recurrence were anastomotic site, peritoneum, lungs and liver, with all cases being detected on surveillance imaging. The shortest time to recurrence was 1 month where the patient was detected to have lung metastasis. Retrospectively, there were some sub-centimetre nodules already present on earlier scans which were too small to definitively diagnose as metastasis at the time of imaging, and these had progressed on the patients post operative scan. Another 2 patients with short DFI

were found to have recurrence in the peritoneum (detected at 3 months), and another in the lung (detected at 5 months). 4 out of these 6 patients had received adjuvant treatment with an average time to chemotherapy of 31.25 days. 2 patients were lost to follow up as they were foreigners. To date, the DFI is calculated at a median of 20.5 (IQR 10-36) months.

Table 1: Characteristics of patients enrolled in this prophylactic HIPEC trial.

Characteristics	No (N=17)
Age	39-77
Gender	Female 7: Male 10
Race	Chinese 11: Malay 2: Others 4
Comorbidities	
- Hypertension	7
- Hyperlipidaemia	5
- Chronic kidney disease	0
- Diabetes	3
- Ischaemic heart disease	0
Group 1 Total	14
- T4 on scan	10
- Peritoneal disease on scan	4
Group 2 Total	3
- Perforated tumour	1
- Peritoneal disease detected	2
PCI score	Median 0 (Range 0-9)

Table 2: Summary of results from the study group.

	Median	IQR
Blood loss (ml)	500	350-750
Clavien-Dindo	0	0-1
LOS (days)	12.5	9-15
LOS SICU (days)	0	0-0
LOS High dependency (HD) (days)	2	2-2
Day to diet	6.5	5-9
Day to CF	2	2-2
Day to FF	4	3-5
Time to chemotherapy (days)	42.5	34.5-51
DFI (months)	20.5	10-36

Abbreviations: CF: Clear Feeds; DFI: Disease-Free Interval; FF: Full Feels; IQR: Interquartile Range; LOS: Length of Stay; SICU: Surgical Intensive Care Unit.

Table 3: Summary of data comparing study group with control.

	Study (N=17)		Control (N=214)		
	Median	IQR	Median	IQR	p
Blood loss (ml)	500	350-750	1000	600-2000	**<0.01**
Clavien-Dindo	0	0-1	0	0-2	0.07
LOS (days)	12.5	9-15	14	11-19	0.06

Abbreviations: IQR: Interquartile Range; LOS: Length of Stay. Numbers in bold indicate statistical significance at p<0.05.

Comparing this group with our control (N=214), we were only able to compare volume of blood loss, LOS and CD score. There was no statistical difference between the 2 groups in terms of LOS and CD score.

Discussion

Prophylactic HIPEC for high-risk CRC has been increasingly investigated, with more studies evaluating its role in the management of peritoneal disease. To our knowledge, there has not been a study done in a tertiary Asian institute looking at the role of prophylactic HIPEC in patients with high-risk of developing PM from CRC. Various trials showed differing results, with some having improved DFI and OS whereas others did not show any difference as compared to standard treatment. Hence, we set out to study this in our group of patients to assess the benefit of prophylactic HIPEC.

In 2019, the COLOPEC trial was published by a Dutch group, recruiting 204 patients from 9 centres in Netherlands, randomising them to either adjuvant HIPEC followed by systemic chemotherapy versus systemic chemotherapy alone [9]. Here they used oxaliplatin as their HIPEC agent, instilling it at 42 degrees for only 30 minutes [9]. The HIPEC procedure was done within 5-8 weeks after initial surgery, as what we have done with our Group 2 patients. They did not manage to show any benefit in DFI and OS. In our small group, we routinely used MMC as our HIPEC agent and this is instilled for 60 minutes. Differences in the HIPEC agent and duration of HIPEC instillation could account for differing results between trials.

On the other hand, PROPHYLOCHIP-PRODIGE 15 study looked at having patients with high-risk features, either randomised to surveillance versus second look surgery with HIPEC following initial surgery and 6 months of adjuvant chemotherapy [10,11]. This study also did not show any significant difference in DFI or OS between the two groups. This was following a study from Elias et al. in 2011 who reviewed the role of second look surgery with HIPEC in patients at high-risk of developing PM [12]. Results of the study were promising, allowing a 90% 5-year OS in their patient cohort. Unfortunately, it is difficult to determine if the early detection and treatment of peritoneal disease from the second look surgery or the HIPEC was to be given credit.

The previous studies mentioned suggested that early detection and management of PM could improve OS. In our current study, we were interested to know if giving upfront HIPEC to high-risk patients, would prevent the occurrence of PM. Sammartino et al. performed a study on 25 patients with T3/T4 disease and mucinous or signet ring cell histology, where these patients underwent upfront resection and HIPEC [8]. No other high-risk features were included such as perforated tumour, presence of limited peritoneal disease, or krukenberg tumours [11]. Their outcomes were compared with matched controls who did not undergo HIPEC and they showed an improvement in local recurrence rates at 48 months (4 vs 28%) [8]. Our study has yet to reach the 5-year mark. With 2 fallouts due to lost to follow up, the minimum follow-up duration is still about 18 months only. Hence, we are not able to make a conclusion on the ability of prophylactic HIPEC in prolonging DFI or OS.

Despite the small number of patients recruited, we had 2 patients with higher morbidity. These were a result of anastomotic leak and pneumonia. Anastomotic leak after a CRS and HIPEC has been reported to occur between 8-12% of patients, with risk factors including male sex, left-sided colorectal resection, prolonged operative time, nutritional status, ECOG status, previous systemic chemotherapy and smoking [13-15]. Our patient who had an anastomotic leak was a female patient aged 55 years, with no significant cardiovascular risk factors. She had no neoadjuvant treatment and had undergone an anterior resection. The second patient had developed postoperative hospital acquired pneumonia requiring SICU admission for 3 days for respiratory support. He had no prior medical illnesses and had undergone a right hemicolectomy with primary ileocolic anastomosis. Our centre's experience on HIPEC with MMC is that the drug is relatively safe with minimal side effects. Hence, we cannot solely attribute this severe morbidity to the HIPEC use itself. The cause of the morbidity was likely to be a multifactorial process.

In the existing literature, both platinum-based and MMC can be used as chemotherapy agents in HIPEC for PM of colorectal origin [16]. HIPEC with MMC was chosen because our unit, in collaboration with the medical oncology department has been utilizing MMC for HIPEC for colorectal PM since 2001. Both agents are cell cycle independent alkylating agents, interfering with DNA and DNA-synthesis [17-19]. Because of its large molecular weight, there is limited systemic absorption of both agents [20]. The enhancement of cytotoxicity under hyperthermia and a maximal tissue penetration of 2-3 mm are also comparable [20]. In many trials, there has not been any clear benefit for HIPEC with Oxaliplatin or MMC. In addition, oxaliplatin is associated with postoperative bleeding as it is known to cause thrombocytopaenia [21]. Whereas for MMC, even though the most common complication would be neutropenia, which occurs in 40% of patients, majority are minor [22]. A study from Tan et al. on chemotherapeutic agents being used in 214 patients undergoing CRS and HIPEC showed that MMC can also cause other complications such as respiratory (17%), intra-abdominal collections (8.8%), anastomotic leak (4.4%), wound infection (7.2%), ileus (6.2%) and ARI (5.6%) [23]. These complications were found to be related to the prolonged surgical time and complexity of the cases performed.

We acknowledge as this is a pilot study, the sample size is small. In addition, 6 of the patients have been found to have recurrences based on follow up imaging within a short period (less than 6 months postoperatively). We are unable to determine the reason for the short interval before recurrence. The hypothesis would involve the tumour biology, one being a mucinous tumour which is relatively less chemosensitive. Another hypothesis would be that lung micro-metastases were already present in the patient with the locally advanced tumour, but was not detectable on initial staging scans, and hence not preventable with the use of HIPEC.

In this group of patients, we managed to achieve time to adjuvant chemotherapy within a median of 42.5 (IQR 34.5-51) days. This is acceptable as most clinical trials of adjuvant chemotherapy in colon cancer require initiation within 6 to 8 weeks after surgical resection [24,25]. Delays to initiation of adjuvant treatment in patients with CRC have been shown to be negatively affect survival [26].

Conclusion

This pilot study shows that prophylactic CRS and HIPEC is feasible in patients with locally advanced CRC presenting with high-risk features for PM, with appropriate time to receiving adjuvant chemotherapy. However, randomised trials would be needed to assess the efficacy in reducing peritoneal disease and recurrence.

Abbreviations: BSA: Body Surface Area; CC: Completeness of Cytoreduction; CC: Clear Feeds; CD: Clavien-Dindo; CRC: Colorectal Cancer; CRS: Cytoreductive Surgery; DFI: Disease-Free Interval; FF: Full Feeds; HIPEC: Hyperthermic Intraperitoneal Chemotherapy; HD: High Dependency; IQR: Interquartile Range; LOS: Length of Stay; MMC: Mitomycin C; OS: Overall Survival; PCI: Peritoneal Carcinomatosis Index; PM: Peritoneal Metastases; SICU: Surgical Intensive Care Unit.

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