Original Article

Short- and Long-term Outcome of Prophylactic Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Preventing Peritoneal Metastasis in Patients with T4 Colorectal Cancer

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Key Words
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Peritoneal metastasis

Purpose. To evaluate short-term and long-term outcomes of prophylactic hyperthermic intraperitoneal chemotherapy (HIPEC) in preventing peritoneal metastasis in patients with T4 colorectal cancer.
Methods. This prospective single-center study was conducted on 17 patients with clinical T4 colorectal cancer without distal organ metastasis or peritoneal metastasis, who underwent curative colon resection surgery combined with prophylactic HIPEC at China Medical University Hospital between January 2017 and December 2021. Exclusion criteria included patients over 75 years old, middle and low rectal cancer cases, patients with synchronous cancer, and those requiring emergent surgery. The observed outcome were peritoneal-metastasis-free survival (PMFS), disease-free survival (DFS), and overall survival (OS). Postoperative complications were recorded to assess safety.
Results. The median age of the 17 patients was 53 years, with 70.6% being female. 52.9% received mitomycin-based HIPEC regimen, and 47.1% received oxaliplatin-based HIPEC regimen. The median observation period was 37.7 months. The 3-year PMFS rate was 94.1%, 3-year DFS rate was 82.4%, and 3-year OS rate was 100%. Postoperative complications were recorded in 3 patients, including anastomotic leakage, intra-abdominal abscess, and acute kidney injury. No 30-day mortality was observed.
Conclusion. Prophylactic HIPEC combined with curative surgery in T4 colorectal cancer patients appears to be a safe and effective strategy for preventing peritoneal metastasis, demonstrating high disease-free survival rates and manageable complications. Further comparative studies are required to confirm these findings and optimize treatment protocols.

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Colorectal cancer (CRC) is a multifactorial malignancy disease and is the third most prevalently diagnosed cancer and the second leading cause of cancer-related deaths globally.[1]

Peritoneal metastasis in patients with CRC remains a significant challenge in oncological therapy.

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It is considered a terminal condition with limited treatment selection and generally represents a shorter overall survival (OS) than other metastasis sites without peritoneum involvement. The OS of patients with peritoneal metastasis only is 16.3 months,[2] which is significantly less than those with liver (19.1 months) and lung metastases (24.6 months).[3] Some studies reveal < 3-6 months of survival from peritoneal metastasis without treatment.[4]

Therefore, developing effective strategies to treat and prevent peritoneal metastasis are pivotal aspect in improving the prognosis of patients with CRC. A recent phase 3 randomized controlled trial (RCT) has emphasized the promising benefits of cytoreduction surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC) in addressing resectable CRC with peritoneal metastasis,[5,6] demonstrating improved OS, compared to systemic treatment.

Patients with T4 CRC may have a high risk of developing peritoneal metastases, with 36% of them expected to suffer from a locoregional or peritoneal recurrence within 3 years after surgical resection.[7] However, the prophylactic role of HIPEC in preventing peritoneal metastasis remains unclear. Several phase 3 RCTs were published but provided opposite results. The HIPECT4 trial presented a positive outcome in the usage of prophylactic HIPEC while improving the locoregional recurrence rate.[4] Meanwhile, prophylactic HIPEC demonstrated no statistical benefit in peritoneal metastasis-free survival (PMFS) in the COLOPEC and PROPHYLOCHIP trials.[8,9]

This clinical study aimed to present the short-term outcome, oncologic results, and clinical safety of prophylactic HIPEC treatment in patients with clinical T4 CRC in our institution.

Materials and Method

Study population and design

This prospective, single-center, single-arm study included patients with cT4 CRC without distal organ metastasis nor peritoneal metastasis who underwent curative colon resection surgery combined with prophylactic HIPEC from January 2017 to December 2021 in China Medical University Hospital (CMUH). Exclusion criteria include (1) age of > 75 years old, (2) middle and low rectal cancer cases, (3) synchronous cancer, and (4) emergent surgery requirements, such as colon perforation, total obstruction, ischemia, etc.

Neoadjuvant chemotherapy for cT4 lesions may be recommended according to our colorectal specialist's judgment. All cancer treatments were based on the CMUH CRC treatment guideline, and colorectal specialists performed all the surgeries. The Institutional Review Board has approved the trial (IRB: CMUH110-REC2-033).

We collected all clinical data from our prospectively recorded databases, including patients' demographics, tumor information, histopathological characteristics, and postoperative clinical and oncologic results.

Intervention: curative surgery with prophylactic HIPEC

Curative surgery involved resecting the colon section that contains the tumor with an adequate tumor-free margin, as well as removing the major vascular pedicle feeding the tumor, along with the regional lymphatic tissue and mesocolon. Omentectomy and appendectomy were then performed as part of the standard procedure for prophylactic HIPEC. Bilateral oophorectomy was also recommended for postmenopausal female patients.

The regimen and dosage of prophylactic HIPEC included two options: (1) oxaliplatin (dose: 460 mg/m^2) for 60 min, combined with intravenous-infusion fluorouracil (dose: 400 mg/m^2) during surgery, and (2) mitomycin C (split dose: first dose: 17.5 mg/m^2, second dose: 8.8 mg/m^2, and third dose: 8.8 mg/m^2, total 35 mg/m^2) for 90 min (split dose every 30 min). The regimen choice was surgeon-dependent.

All curative surgery and prophylactic HIPEC treatment were introduced to the patients preoperatively, who then signed the surgical informed consent.

Postoperative care and adjuvant chemotherapy

Postoperative ward care was provided as rou-

tine. Any surgical-related complications were recorded. The patients were arranged to receive scheduled adjuvant chemotherapy as part of their treatment plan, including 8 cycles of CAPOX or 12 cycles of mFOLFOX6, postoperatively. Subsequently, they were scheduled for regular follow-up appointments in the outpatient department (OPD) to monitor the treatment efficacy and recurrence conditions. The follow-up evaluations were arranged every 3 months for the first 2 years, then every 6 months for the next 3 years. Routine blood tests, tumor markers, including CEA and CA-199, and image examinations were conducted regularly during the observation period. All complications, recurrence, or distal metastasis occurring postoperatively were recorded in the OPD clinic.

Observed outcome

The main observed outcome in this study was to assess the short-term and long-term outcome of prophylactic HIPEC in high-risk patients with T4 CRC. The short-term outcome included the length of hospital stay, postoperative complication and mortality within 30 days, and the re-admission rate. Complication events were assessed to determine the safety and feasibility of prophylactic HIPEC surgery. The long-term outcome included the peritoneal-metastasis-free survival (PMFS), disease-free survival (DFS), and overall survival (OS).

Peritoneal metastasis, local recurrence, or distal metastasis was diagnosed based primarily on imaging examination, including abdominal sonography, computed tomography scans, and positron emission tomography scans. Laparoscopic examination may help in early metastasis which was highly suspected.

Peritoneal metastasis was defined as any sign of cancer cells spreading to the peritoneal cavity, forming metastatic deposits on the peritoneal surfaces. Conversely, local recurrence refers to cancer reappearance at or near the original primary tumor site after treatment. The location may depend on the primary tumor site, such as on the sacrum, duodenum, and paracolic sulcus for rectal, colon, and left colon cancers, respectively.

Statistical analysis

Statistical analysis for measurement data of normal distribution was represented by mean (standard deviation), and the non-normal distribution data was represented by median (interquartile range [IQR]). The qualitative data was presented as frequency (%). The Kaplan-Meier curve was used for survival analysis. Statistical Package for the Social Sciences (SPSS) version 25 for Windows (IBM, Armonk, NY) was used for all data analyses.

Results

A total of 124 patients who were initially diagnosed with cT4 CRC, without peritoneal metastasis and distant metastasis, underwent curative colon resection surgery at CMUH from January 2017 to December 2021. Among them, 17 agreed to join the study preoperatively. The 17 patients underwent appropriate preoperative assessment and then received prophylactic HIPEC combined with curative colon resection surgery. Fig. 1 illustrates the patient enrollment.

Patient baseline characteristics

Table 1 shows the baseline characteristics of 17 enrolled patients. Of them, 76% were female. The median age of enrolled patients was 53 years old. Con-

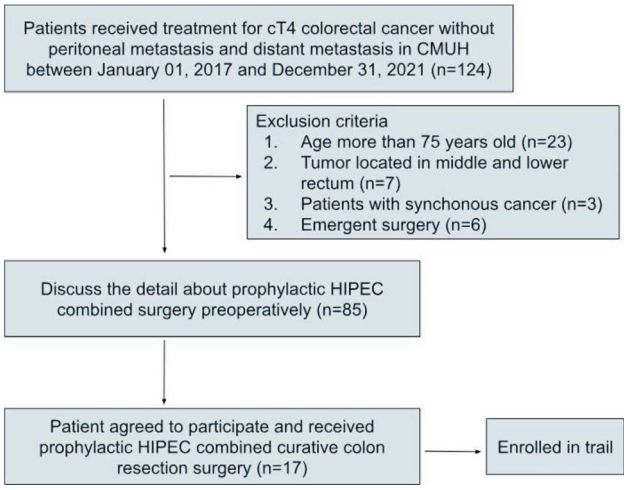

Fig. 1. Flowchart for patient enrollment.

sidering the primary tumor site, 7 patients have right-side colon cancer, whereas 9 patients have left-side colon cancer, and 1 has upper rectal cancer. In this study, 52.9% of patients received a mitomycin-based regimen, whereas 47.1% received an oxaliplatin-based regimen as a prophylactic HIPEC regimen.

Postoperative clinicopathological characteristics

Table 1 lists postoperative clinicopathological characteristics. According to the pathology report, 10 and 7 patients were categorized into pT4a and pT4b, respectively. No lymph node metastasis was found in 8 patients (N0), whereas 9 patients exhibited lymph node metastasis (N1/N2). Among the 17 patients, 16 were adenocarcinoma type and 1 was mucinous type. High microsatellite instability (MSI-H) was observed in 4 (23.5%) patients. After the curative surgery, 16 patients received a whole course of standard adjuvant chemotherapy, whereas 1 patient refused any type of adjuvant chemotherapy.

Safety and adverse events

Table 2 shows short-term outcomes. The median length of hospital stay is 11 days (IQR: 3 days). Post-operative complications within 30 days postoperatively were found in 3 (17.6%) patients, including 1 with anastomosis leakage and needing re-operation, 1 with intraabdominal abscess formation, and 1 with acute kidney injury (AKI). This study revealed no postoperative 30-day mortality. Re-admission within 30 days was recorded in 1 case, which resulted from intraabdominal abscess formation.

Long-term outcome

Table 3 shows long-term outcomes. The median observation period was 37.7 months (IQR: 26.35-

Table 1. Baseline characteristics

	Prophylactic HIPEC (n = 17)
Cases (n)	17
Median age (IQR)	53 (9)
Gender, n (%)	
Male	5 (29.4%)
Female	12 (70.6%)
Primary tumor site, n (%)	
Right side colon	7 (41.2%)
Left side colon	9 (52.9%)
Rectum	1 (5.9%)
T category, n (%)	
T4a	10 (59.8%)
T4b	7 (41.2%)
N category, n (%)	
N0	8 (47.1%)
N1/N2	9 (52.9%)
MSI, n (%)	
MSI-L/MSS	13 (76.5%)
MSI-H	4 (23.5%)
Histology, n (%)	
Adenocarcinoma	16 (94.1%)
Mucinous/Signet ring cell carcinoma	1 (5.9%)
HIPEC regimen, n (%)	
Mitomycin C-based regimen	9 (52.9%)
Oxaliplatin-based regimen	8 (47.1%)
Adjuvant chemotherapy, n (%)	
mFOLFOX6	16 (94.1%)
No	1 (5.9%)

Table 2. Short term outcome and post-operative complication in 30 days

	Prophylactic HIPEC (n = 17)
Length of hospital stay: median (IQR), d	11 (3)
Major complication (Clavien-Dindo classification ≥ III), n (%)	1 (5.9%)
Anastomotic leakage	1
Minor complication (Clavien-Dindo classification < III), n (%)	2 (11.8%)
IAI	1
AKI	1
Mortality in 30 days, n (%)	0
Readmission within 30 days, n (%)	2 (11.8%)

Table 3. Long term result – free survival

	Prophylatic HIPEC (n = 17)
Peritoneal metastasis	
No	16 (94.1%)
Yes	1 (5.9%)
Distal metastasis	
No	15 (88.2%)
Yes	2 (11.8%)
Site of metastasis	
Liver with peritoneal metastasis	1
Liver alone	1
Lung/other organ	0
Local recurrence	1 (5.9%)
Mortality	0
Peritoneal-metastasis-free survival (PMFS), mean (95% CI), m	61.43 (54.46-68.40)
Disease-free survival (DFS), mean (95% CI), m	54.94 (44.54-65.33)
Overall survival rate	100%
Follow up period, median (range), m	37.7 (1.6-65.1)

54.45 months). All patients remained alive at the end of the observation period (January 31, 2024). Recurrence occurred in 3 patients during the observation period. One patient was diagnosed with peritoneal metastasis. Two cases demonstrated distal organ metastases, including 1 developing liver metastasis with peritoneal metastasis and 1 with liver metastasis alone. One case exhibited local recurrence. The 3-year PMFS rate was 94.1% (Fig. 2A). The mean PMFS was 61.43 months (95% confidence interval [CI]: 54.46-68.40 months). The 3-year DFS rate was 82.4% (Fig. 2B). The mean DFS was 54.94 months (95% CI: 44.54-65.33 months). The OS rate was 100%. The patients with any type of recurrence were treated based on CMUH guideline recommendations.

Univariable analysis for DFS was calculated with Cox regression (Table 4). Several prognostic factors were discussed, including gender, primary tumor location, pT stage, N stage, MSI status, and prophylactic HIPEC regimen selection. However, univariable analysis revealed that the factors did not present any statistically significant difference in DFS.

Discussion

Locally advanced CRC, particularly those classified as T4 stage, are recognized as high-risk for developing subsequent peritoneal metastasis. Therefore, several ongoing researches aimed at preventing peritoneal metastasis in patients with advanced CRC by prophylactic HIPEC. Our study revealed that only 5.7% of patients with T4 tumors developed peritoneal metastasis after prophylactic HIPEC with 82.4% of 3-year DFS and 94.1% of 3-year PMFS. Surgical morbidity was only 17.6% and only 5.7% of patients experienced major complications. No death event was reported during our observed period.[10]

Efficiency of prophylactic HIPEC

This single-arm study endeavored to combine curative surgery with prophylactic HIPEC in patients with cT4 CRC. Considering the current research literature, the efficacy of prophylactic HIPEC in contributing to improving oncological survival in patients with high-risk CRC remains debatable. The HIPEC4 trial, a randomized controlled multicenter study conducted in Spain, reported a 3-year DFS rate of 81.2% for the group receiving prophylactic HIPEC, compared to 78.0% for the control group. Additionally, the locoregional control rate in the HIPEC group was 97.6%, which was significantly higher than the 87.6% observed in the control group. Therefore, the HIPEC4 trial concluded that prophylactic HIPEC improved the locoregional control rate, and a longer follow-up pe-

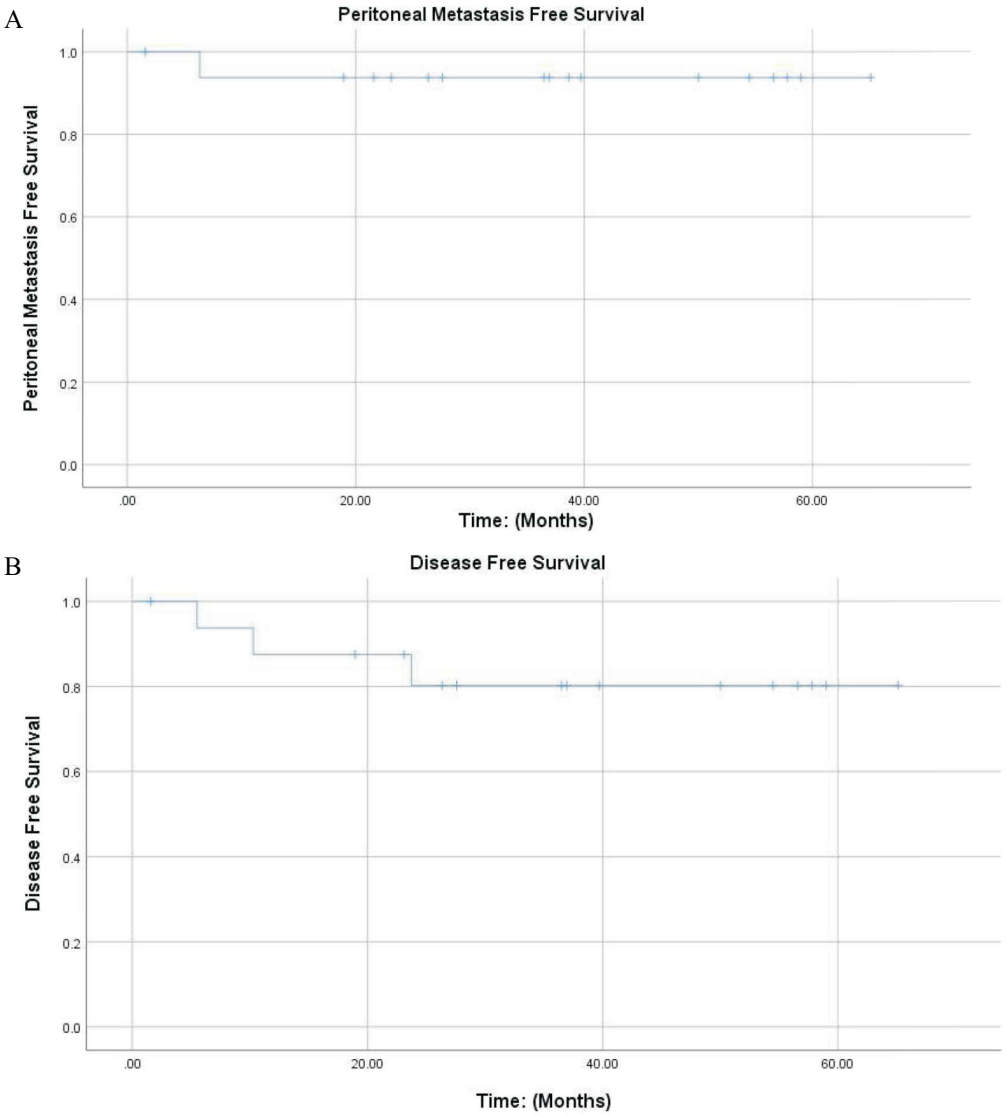

Fig. 2. A. Peritoneal metastasis free survival. B. Disease-free survival.

Table 4. Univariable analyses of prognostic factors influencing DFS

Variables	Univariate analysis	
	HR (95% CI)	*p* value
Gender (Male vs. Female)	0.026 (0.000-654.622)	0.482
Tumor location (Right vs. Left)	0.317 (0.028-3.529)	0.350
pT stage (pT4a vs. pT4b)	0.007 (0.000-139.098)	0.338
N stage (N0 vs. N1-2)	1.914 (0.173-21.132)	0.596
MSI (MSI-L/MSS vs. MSI-H)	5.536 (0.017-1806.49)	0.562
HIPEC regimen (Mitomycin C vs. Oxaliplatin)	1.574 (0.142-17.395)	0.711

riod remains required to assess the OS following prophylactic HIPEC in patients with T4 CRC.[11]

Contrastingly, the COLOPEC trial, another RCT from the Netherlands for the role of prophylactic HIPEC in patients with CRC with T4 lesions or tumor perforation, drew a different conclusion. The 5-year PMFS was 63.9% in the HIPEC group, compared to 63.2% in the control group, after a median observa-

tion period of 54 months. The 5-year DFS was 55.7% and 52.3% in the HIPEC and control groups, respectively. The 5-year OS was 69.6% in the HIPEC group, while it was 70.9% in the control group. No significant improvements were seen with the addition of prophylactic HIPEC in terms of PMFS, DFS, or OS after five years compared to curative surgery alone. Noteworthily, the COLOPEC study revealed that 91% of the patients received the HIPEC infusion 5-8 weeks after curative surgery, whereas only 9% of patients received prophylactic HIPEC simultaneously with the curative surgery.[12] Additionally, the regimen in the COLOPEC trial involved an intraperitoneal oxaliplatin infusion for only 30 min, concurrently with intravenously administered fluorouracil/leucovorin. A longer duration for the oxaliplatin infusion may be required for potential efficacy improvement.[13]

The PROPHYLOCHIP trial from France investigated the necessity of second-look laparoscopic diagnosis surgery with prophylactic HIPEC in patients with CRC with high-risk PM, such as resected initial peritoneal metastasis, resected ovarian metastasis, and tumor perforation, after six months of adjuvant chemotherapy.[14] The results indicated that the 3-year DFS rate for patients undergoing second-look surgery and prophylactic HIPEC was 44% (95% CI: 33%-56%), compared to 53% (95% CI: 41%-64%) for the control group who did not undergo additional prophylactic surgery. However, no significant difference in 3-year DFS was observed between the prophylactic HIPEC group and control groups postoperatively.

Safety and complication

Our study documented, regarding the safety of prophylactic HIPEC, that two (11.8%) patients experienced minor complications (Clavien-Dindo grades 1 and 2), which included an intraabdominal abscess and AKI. Additionally, 1 (5.9%) patient encountered a major complication (Clavien-Dindo grades 3 and 4) of anastomosis leakage, which required re-operation. Notably, our study reported no occurrence of 30-day mortality.

In comparison, the HIPEC4 trial reported that major complications occurred in 21 out of 89 (23.6%) patients in the prophylactic HIPEC group within 30 days, compared with 17 out of 95 (17.9%) patients in the control group. This rate is higher than observed in our study. Specifically, AKI was noted in one patient in the HIPEC group, with no cases in the control group. Anastomosis leakage occurred in 6 (6.7%) and 9 (9.5%) patients in the HIPEC and control groups, respectively.[13] Furthermore, the COLOPEC trial indicated a major complication rate of 10% in the prophylactic group, versus 3% in the control group.[13]

The incidence of AKI is a significant concern in HIPEC procedures due to the potential nephrotoxicity of chemotherapeutic agents used, considering the complications encountered in our study. A study revealed that AKI may occur in up to 31.8% of patients undergoing HIPEC,[15] particularly higher in patients treated with cisplatin-containing HIPEC regimens. Conversely, previous hypotheses assumed that the anastomosis leakage may be associated with HIPEC infusion. However, recent studies indicated a comparable overall anastomosis leakage rate after HIPEC to that observed following conventional colorectal surgery after colorectal surgery, with no cumulative risk of multiple anastomoses.[16] Therefore, prophylactic HIPEC may contribute to a higher risk of AKI, but it may be invaluable for performing extra measurements to prevent anastomotic leakage after prophylactic HIPEC. Further research needs to address these complications explicitly to improve the safety and efficacy of HIPEC as a preventative strategy for peritoneal carcinomatosis.

Short-term major postoperative complications (grades 3-4) occurred in 41% of patients (29 out of 71) who underwent second-look surgery and prophylactic HIPEC, as discussed in the PROPHYLOCHIP trial.[14] The extended operation time and the necessity for the second surgical procedure may have negatively affected the complications. Given the high complication rate and the absence of a significant improvement in 3-year DFS reported in the PROPHYLOCHIP trial, it may not be recommended to perform additional second-stage prophylactic HIPEC surgery in patients with high-risk CRC who demonstrate no signs of recurrence after completing curative surgery and systemic treatment.

Regimen and procedure

Our study administered oxaliplatin-based or mitomycin C regimens to 8 and 9 patients, respectively. The selection of the chemotherapeutic regimen should balance efficacy and safety to optimize patient outcomes. Several previous researches are still discussing both oxaliplatin or mitomycin C administration. Hübner et al. (2022) have indicated in a recent study that mitomycin C (infusion for 90 min, three fractions) may be a better choice over oxaliplatin-based regimen due to better effectiveness in peritoneal carcinomatosis control and relative minimal morbidity.[17] Ongoing clinical studies may be warranted to help standardize HIPEC methodology and regimens in the future.

Limitation

This study encounters several limitations that must be acknowledged. First, the small sample size not only limited the generalizability of our results but also restricted the ability to conduct further subgroup analyses. Second, a comparator group was lacking in the single-arm design, which is crucial for establishing a robust comparison and understanding the true efficacy of the intervention. Third, the research was limited to patients with T4 staging, whereas more high-risk factors for peritoneal metastasis in CRC can also be discussed, including colon perforation, tumor obstruction, poorly differentiated histology, mucinous or signet-ring cell histological subtypes, BRAF mutation, etc. Fourth, the short observation period limits the assessment for long-term survival outcomes. Addressing these limitations in future research will be crucial to discover the therapeutic potential of prophylactic HIPEC in the patient population.

Conclusion

The use of prophylactic HIPEC in patients with T4 locally advanced CRC remains controversial, but the survival outcomes from our single-arm study are quite impressive. Additionally, we revealed a relatively tolerable and low complication rate, which indicates an efficient safety for prophylactic HIPEC. However, continued comparative analyses and pooling of data from similar studies are essential due to the lack of robust evidence. These efforts are crucial for refining treatment protocols, optimizing chemotherapy regimens, and establishing comprehensive long-term patient follow-up strategies.

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原　著

預防性腹腔內熱化療用於預防 T4 期大腸癌患者之腹膜轉移：短期與長期治療效果

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前言　結直腸癌 (CRC) 是導致癌症相關死亡的主要原因之一，其中腹膜轉移因治療選擇有限和生存率低而成為目前醫療上的重大挑戰。本研究主旨為探討在高腹膜轉移風險的 T4 期結直腸癌病人身上，使用預防性腹腔內熱化療 (HIPEC) 的短期安全性與長期治療成效。

方法　這是一項前瞻性單中心研究，研究對象為 17 名被診斷為臨床 T4 期結直腸癌，且無遠端器官轉移或腹膜轉移之患者。這些患者於 2017 年 1 月至 2021 年 12 月期間在中國醫藥大學附設醫院接受根治性結腸切除手術並合併預防性腹腔內熱化療。排除標準包括年齡超過 75 歲、中低位直腸癌病例、同時併存有其他種癌症、及接受緊急手術的患者。觀察指標為無腹膜轉移生存期 (PMFS)、無疾病生存期 (DFS) 和總生存期 (OS)。同時為了評估預防性腹腔內熱化療之安全性，研究中也同步紀錄術後相關併發症。

結果　17 名患者的年齡中位數為 53 歲，其中 70.6% 為女性。在施行預防性腹腔性熱化療的劑型方面，有 52.9% 的病人使用 Mitomycin-C，而 47.1% 接受了 Oxaliplatin。觀察期中位數為 37.7 個月。3 年無腹膜轉移生存率為 94.1%，3 年無疾病生存率為 82.4%，3 年總生存率為 100%。有 3 例個案出現術後併發症，包括吻合口滲漏、腹腔內膿瘍和急性腎損傷。無任何病患於 30 天內死亡。

結論　對於 T4 期別之結直腸癌患者而言，預防性腹腔內熱化療結合大腸癌切除根治性手術呈現出令人印象深刻的臨床結果，包括三年無疾病生存率高達 82.4%、以及相當低的併發症率。因此以預防性腹腔內熱化療降低未來腹膜轉移機率，似乎是有發展性且安全的治療選擇。然而，由於缺乏證據證明預防性腹腔內熱化療帶來更佳的預後，未來需要進一步加入對照組進行比較性研究以確認其控制腫瘤復發之療效。

關鍵詞　大腸直腸科、手術、預防性、腹腔熱化療、腹膜轉移。