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REVIEW ARTICLE

# Recent Update on the Treatment of Colorectal Peritoneal Metastasis: A Surgical Perspective

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Colorectal peritoneal metastasis has been an incurable disease for centuries. However, since the new millennium, recent advancements in therapies are achieved with modern chemotherapeutic agents, target agents, and immune checkpoint blockade introduction. Modern chemotherapies, from a nearly nonexistent median survival if untreated, have raised the duration to 16 months with target agents. Experts have once again surpassed its limit by introducing intraperitoneal chemotherapy and cytoreductive surgery (CRS). Numerous clinical trials regarding CRS and hyperthermic intraperitoneal chemotherapy have now opened new doors in peritoneal carcinomatosis treatment, even securing complete remission. In addition, up-to-date modalities, such as pressurized intraperitoneal aerosol chemotherapy and immunotherapies, showed promising results at an early stage.

**Key Words:** Colorectal neoplasm; Peritoneal neoplasms; Cytoreductive surgery; Hyperthermic; Intraperitoneal chemotherapy

## INTRODUCTION

Colorectal peritoneal metastasis (CPM) occurs in approximately 10 to 15% and its prognosis is worst among stage IV colorectal cancer. Since the first randomized controlled trial (RCT) regarding the effect of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) and systemic chemotherapy (SC) demonstrated favorable oncologic outcomes in the former (disease specific survival rate 22.4 months vs. 12.6 months), HIPEC centers around the world have supported this procedure as one of the treatment strategies in CPM [1]. Although three consecutive RCTs regarding Oxaliplatin-HIPEC failed to prove its usefulness in CPM, many specialized centers are still performing Mitomycin-based or Mitomycin/Cisplatin-based HIPEC [2-4]. Even though the HIPEC procedure itself is accompanied by more complications than other general surgeries, it may be a treatment of choice for a carefully selected patients with CPM.

## MAIN SUBJECTS

### Prognosis of Colorectal Peritoneal Metastasis

According to the recent national cancer registry of 2019, the incidence of colorectal cancer (CRC) in Korea is increasing making the 4th most common type of cancer diagnosed [5]. The 5-year relative survival of CRC patients increased to 75.0% in 2015 from its mere 58.7% in 2000. Although the advent of chemotherapy and target agents have improved the prognosis of local and regional stage CRC, those with distant metastasis and CPM are still at its mere 19.8% [6]. Pre-oxaliplatin era showed a median survival of 8.9 months in CPM patients, which doubled to 16.3 months after the introduction of oxaliplatin, irinotecan, and targeted agents, such as bevacizumab and cetuximab [7]. Five-year overall

survival even with modern chemotherapeutics is less than 5% [8]. Peritoneal metastasis is the third most common organ of metastasis next to liver and lung, accounting for 11% of CRC patients [9]. Once believed to be a systemic disease, some surgical oncologists now believe it to be a loco-regional disease warranting loco-regional treatment with emerging ideas that surgical approach to CPM patients may be a treatment option given the poor prognosis with intravenous (IV) therapeutics. Resection of liver metastasis in CRC patients have been the only treatment with curative intent with a 5-year survival rate of nearly 40% compared to the near zero with medical interventions [10]. Sugarbaker, a pioneer of HIPEC, extended the concept to peritoneal metastasis arguing for surgical resection of CPM [11].

In 1996, a French group of colorectal surgeons led by Elias initiated a trial with a working hypothesis that a previous 2-year survival rate of 10% could be increased to 40% with complete cytoreduction followed by early postoperative intraperitoneal chemotherapy (EPIC) [12]. After undergoing CRS, patients were randomized to a control group of SC (5-fluorouracil, 5-FU) and an experimental group of EPIC (mitomycin C, MMC). The results were shocking to the medical community as both groups showed unexpectedly high overall survival rate of 60% at 2 years, compared to the previously known 10% when treated only with SC. Although deemed as a failed trial with early termination due to failed patient recruitment, Elias' trial provided a stepping stone for the efficacy and benefits of CRS in CPM patients, which convinced some surgical oncologists to believe that CPM could be a loco-regional disease.

## Rationale for HIPEC

The idea of HIPEC rose from the rationale behind the peritoneal plasma barrier. It slows down the clearance of chemotherapy within the peritoneal cavity exposing remnant tumor cells to chemotherapy for longer periods of time [13]. The peritoneum is a semi-permeable membrane

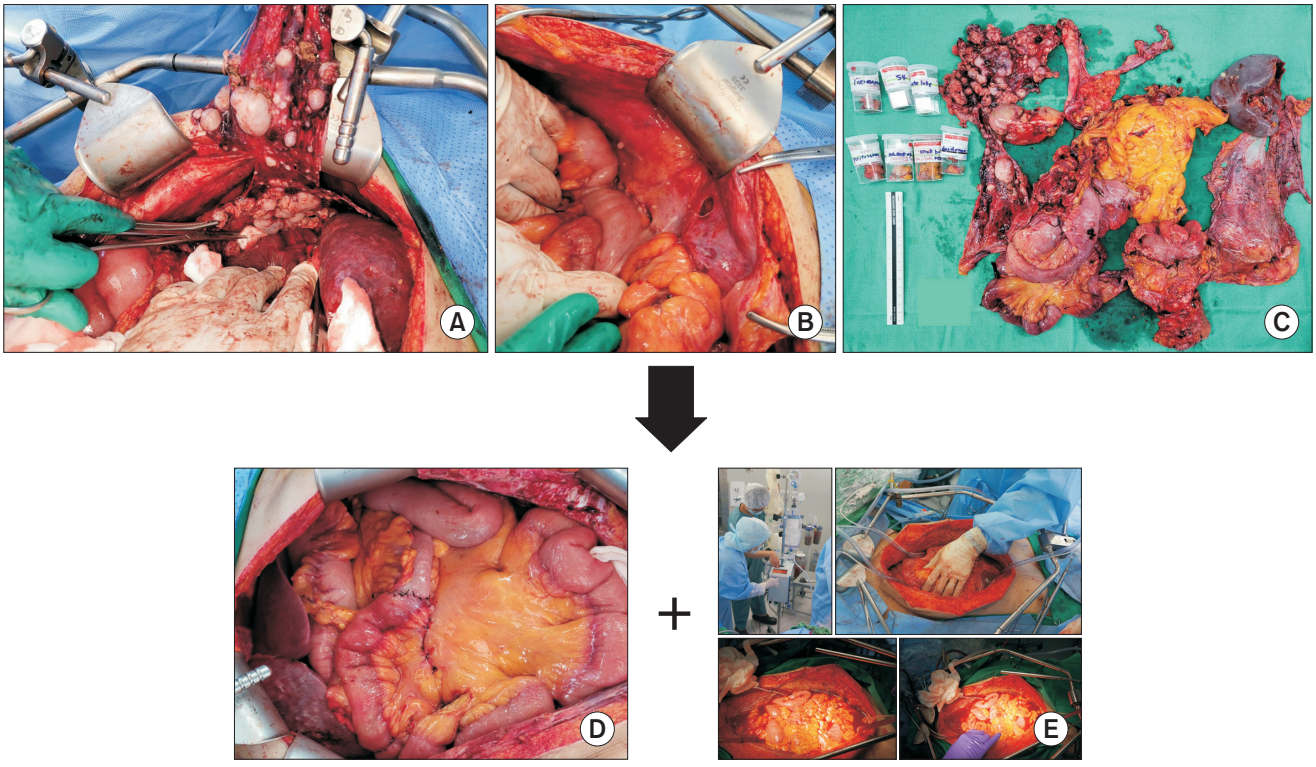


**Fig. 1.** CRS and HIPEC. (A) Peritoneal metastasis. (B) Pelvic peritoneum metastasis. (C) Specimen after complete cytoreduction. (D) After CRS (CC0). (E) HIPEC in open method. CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy.

that surrounds the internal organs to form a space called peritoneal cavity. A large number of immune cells including dendritic cells, T-cells and various soluble factors exist in the peritoneal cavity to fight against various pathogens and cancer. In the process of peritoneal metastasis, tumor cells invade into the peritoneum and form tumor microenvironment to avoid the immune-surveillance making the extermination of these cells even more challenging. There are also reports of prolonged duration of therapeutic agent within the peritoneal cavity via the peritoneal-plasma gradient when bidirectional intraperitoneal and IV chemotherapy are introduced concurrently known as "bidirectional chemotherapy." These characteristics make intraperitoneal chemotherapy an ideal solution for peritoneal metastasis; however, numerous factors need to be considered when performing HIPEC: *method, duration, temperature, choice of chemotherapeutic agent, carrier solution, and timing*.

Currently, open "Coliseum" technique introduced by Sugarbaker is the most common method of HIPEC practiced by experts around the world (Fig. 1E) [11]. Closed technique with catheters and temperature probes is also a popular method of choice. Duration of HIPEC varies by institutions between 30 to 120 minutes, but the temperature is quite standard at 41 to 43°C [14]. Chemotherapeutic agents used in HIPEC procedure is one of the most debated issues for CPM today. Molecular weight, affinity to lipids, direct cytotoxic effect, and systemic toxicity to patients need to be considered [13-15]. For CPM, most widely used chemotherapeutic agents are 5-FU, MMC, and platin derivatives.

It is important to emphasize that CRS does not equal HIPEC, and that the two therapies can work as a synergy but should not be equated as the same. The greatest disadvantage of intraperitoneal chemotherapy is the depth of tissue penetration. Depth of penetration of intraperitoneal chemotherapy has been estimated to be 3 to 5 mm by animal studies [16-19]. Sugarbaker in his early review stated the penetration of depth to be 1 to 2 mm [20]. With the introduction of Peritoneal cancer index (PCI) and completeness of cytoreduction score (CC score) by Sugarbaker, the maximum diameter of residual tumor nodule of 2.5 mm is set as a limit for the consideration of performing HIPEC after CRS [11,21]. The patients' abdomen is divided into nine quadrants, and small bowel is divided into four sections each designated a value from 0 to 3 summing to a total value of 39. Only when CC 0 (no residual disease) or CC 1 (remnant disease less than 2.5 mm) is achieved is HIPEC performed expecting maximum results (Fig. 1).

## Clinical Trials: SC vs. CRS and HIPEC

The first clinical trial compared conventional chemotherapy versus CRS followed by HIPEC. While the previously mentioned French trial [12] compared SC versus intraperitoneal chemotherapy in patients who all underwent cytoreduction, Verwaal et al. [1] compared SC versus CRS and HIPEC (Mitomycin C 70 mg maximum over 90 minutes). With 44 patients in the standard chemotherapy group and 49 patients in CRS and HIPEC group, the median survival was 12.6 months vs. 22.4 months ($p = 0.032$). An 8-year follow-up of the patients showed a median progression-free survival of 7.7 months in the standard group compared to 12.6 months in the CRS and HIPEC group ($p = 0.032$) [22]. However, the trial was conducted before modern chemotherapy agents were introduced; the standard chemotherapy used in this trial was 5-FU and leucovorin.

Franko et al. [23] tried to update the results with modern chemotherapeutics through a non-randomized study. Control group received SC consisted of 5-FU, irinotecan, oxaliplatin, and target agents while 67 patients underwent CRS and HIPEC (Mitomycin C 40 mg over 100 minutes). Compared to the previous median survival of 12.6 months in the Dutch clinical trial using 5-FU regimen, the modern chemotherapy prolonged the duration to 16.8 months. When CRS and HIPEC were performed, the duration doubled to 34.7 months ($p < 0.001$).

Almost identical case-control study was conducted by Elias comparing modern day SC with CRS plus HIPEC and SC with the only difference in HIPEC regimen (oxaliplatin 460 mg/m$^2$ over 30 minutes) [24]. The median survival reported was none we have seen before with 23.9 months in the SC group and 62.7 months in the HIPEC group ($p < 0.05$).


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## Clinical Trials: Second-look and Prophylactic HIPEC

The importance of complete cytoreduction in the prognosis of CPM patients is now a concrete phenomenon embraced by colorectal surgeons worldwide. In order to achieve complete cytoreduction, the extent of the peritoneal disease calculated by PCI is crucial. PROPHYLOCHIP trial aimed to determine if early detection of CPM would make a difference in oncologic outcomes since CPM is difficult to detect via imaging studies [2]. Therefore, this trial performed a second-look surgery for early detection in high risk patients proned to CPM and carried out CRS with HIPEC when the CPM was detected. Three-year disease-free survival for the standard surveillance group was 53% compared to the second-look plus HIPEC group of 44% with no benefit in the later.

A group in the Netherlands performed a multicenter, open-label, randomized trial (COLOPEC) aimed to determine the effectiveness of adjuvant HIPEC in high-risk patients at follow-up of 18-months [3]. Patients with T4N0-2M0 stage or perforated colon cancer were randomized to adjuvant HIPEC with SC and SC alone. There was no difference in peritoneal-free survival at 18-months between the two groups (80.9% vs. 76.2%).

Through both trials, an important issue can be addressed: patient selection. Determining who can best benefit from HIPEC is the ultimate goal in maximizing the effect of HIPEC.

## Lessons from PRODIGE7

The combination of CRS and HIPEC has been believed to provide long-term survival for selected patients diagnosed with either primary peritoneal cancer or peritoneal carcinomatosis secondary to colorectal or ovarian cancer. However, since the HIPEC procedure was accompanied by more complications than other general surgeries, many surgical oncologists began to wonder on the extent of oncologic outcomes of HIPEC outweighing the complications.

PRODIGE 7 study was a randomized, open-label, phase 3 multicenter trial which compared CRS with or without oxaliplatin-based HIPEC among patients diagnosed with peritoneal carcinomatosis originating from CRC [4]. The interest in the results of PRODIGE 7 came from the recent phase 3 clinical trial comparing interval CRS with or without HIPEC in ovarian cancer concluding that HIPEC did not increase complication rate and the addition of HIPEC increased median recurrence-free survival by 3.5 months and median overall survival by 11.8 months compared to the non-HIPEC group [25]. However, this study did not show overall survival benefit of HIPEC to CRS alone (median overall survival 41.7 months vs. 41.2 months, hazard ratio [HR] 1.00 [95% confidence interval, CI 0.63–1.58], p = 0.99; relapse-free survival 13.1 months vs. 11.1 months, HR 0.91 [95% CI 0.71–1.15], p = 0.43), but rather increased 60-day complications in the HIPEC group.

Although it is the most recent update to the field of CPM, few limitations are apparent. Methodological weakness is present from over estimation of the benefit of HIPEC from 30 months in the control arm to 48 months for the experimental arm underpowering the trial. Previous trials by Verwaal et al. [1] and Elias et al. [12] have already proven the oncologic outcome of CRS; therefore, hypothesizing that a single oncologic benefit of HIPEC of 18 months in overall survival may have been a reach. Moreover, the inclusion criteria included patients with extensive disease with PCI value ≤ 25, of which 25% had a PCI value ≥ 16. The duration of HIPEC as well as the regimen of choice (30 minutes, Oxaliplatin) was controversial as perfusion period was 90 minutes in most randomized controlled trials regarding CRS-HIPEC for ovarian and CRC in basis of the fact that optimal regression occurred when the cancer was placed in a heat of 40°C for 90 minutes in a mouse experiment. Nonetheless, a subgroup analysis of overall survival in the group with PCI between 11–15 favored HIPEC (median overall survival 41.6 months vs. 32.7 months, p = 0.0209), but a small sample size of 46 patients (out of 265) precluded the authors from making a concrete conclusion.

François Quenet insisted that CRS alone should be the cornerstone of therapeutic strategies with curative intent for CPM without HIPEC. Expert groups suggested that CRS with mitomycin C-based HIPEC should still be considered

as the recommended treatment for resectable low-volume peritoneal metastasis for colon cancer until other randomized controlled trials (NCT05250648) are conducted.

## Future Endeavors: PIPAC, Immunotherapy

There are still long ways to go until a firm consensus can be made. The method of HIPEC (Open vs. closed), the regimen of chemotherapy (Oxaliplatin vs. MMC), the duration of HIPEC (30 minutes vs. 90 minutes), and most importantly the selection of patients eligible for CRS and HIPEC are a glimpse of what awaits to be explored further in the future. The last three clinical trials [2-4] chose oxaliplatin as a regimen of choice for HIPEC with no definite benefit warranting future clinical trials with MMC. Ongoing clinical trials, such as GECOP-MMC and ICARuS trial may shed some light to the controversies still at hand [26,27].

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a novel delivery technique under copious amount of research today. As CRS and HIPEC have a morbidity rates upto 67.6% and mortality upto 9%, the reduction in complication rates has been a nightmare for most colorectal surgeons [28-31]. PIPAC overcomes such issue by showing minimal adverse effects assuring its safety [32]. Patients tolerate the procedure well as only laparoscopic manipulation is needed allowing multiple rounds of PIPAC possible for a single patient. Girshally et al. [33] conducted a study in which PIPAC was used in neoadjuvant setting allowing for once untreatable patients into an eligible group for CRS and HIPEC. Clinical trials are ongoing, but we are hopeful that PIPAC will expand the pool of CPM patients eligible for a cure.

Even though CRS and HIPEC has improved oncologic outcomes in peritoneal carcinomatosis of colorectal and ovarian cancer, it is still regarded as intractable disease. CRC is a representative of low immunogenic tumor, and attempts are currently being made to transform it into a high immunogenic tumor in many animal experiments (e.g., oncolytic virus, chimeric antigen receptor [CAR]-T cell, Stimulator of interferon genes [STING] agonist). Oncolytic virus and CAR-T cell therapy are methods that directly attack the tumor and expose a large amount of tumor associated antigen to antigen-presenting cells. STING agonist is a target for type I interferon that stimulates the innate immune system

**Table 1.** Summary of clinical trials regarding EPIC/HIPEC

| Author (yr) | Country | Experimental vs. Control | IP agent | Primary end point | Result |
|---|---|---|---|---|---|
| Elias et al. [12], 2004 | France | CRS + EPIC + Systemic CTx. vs. CRS + Systemic CTx | MMC on POD 1 and 5-FU on POD 2-5 | Overall survival | OS of 60% at 2 yr for both groups |
| Verwaal et al. [1], 2003/Verwaal et al. [22], 2008 | Netherlands | CRS + HIPEC vs. Systemic CTx | MMC 17.5 mg/m$^2$ followed by 8.8 mg/m$^2$ every 30 min, total 90 min | Overall Survival | Median survival 22.3 mo vs. 12.6 mo |
| Klaver et al. [3], 2019 | Netherlands | Adj.HIPEC + Systemic CTx. vs. Systemic CTx | 5FU-IV and Oxaliplatin IP (460 mg/m$^2$), 30 min | Peritoneal-free survival at 18 mo | No superiority of adj. HIPEC in high risk group at 18 mo |
| Goéré et al. [2], (2020) | France | Second look surgery + HIPEC vs. Surveillance | Ox 460 mg/m$^2$, 30 min<br>Ox 300–360 mg/m$^2$ + IR 200 mg/m$^2$, 30 min<br>MMC 35 mg/m$^2$ | 3-yr disease-free survival | Failed to improve survival |
| Quenet et al. [4], 2021 | France | CRS + HIPEC vs. CRS alone | Ox 360 or 460 mg/m$^2$, 30 min | Overall survival | No definite benefit in addition of HIPEC |

EPIC, early postoperative intraperitoneal chemotherapy; HIPEC, hyperthermic intraperitoneal chemotherapy; CRS, cytoreductive surgery; CTx., chemotherapy; Adj., adjuvant; MMC, mitomycin C; POD, postoperative day; 5-FU, 5-fluorouracil; IV, intravenous; IP, intraperitoneal; Ox, oxaliplatin; IR, irinotecan; OS, overall survival.


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leading to sensitization of T cells and dendritic cells to cancer. When these drugs are injected intraperitoneally into peritoneal carcinomatosis of colorectal cancer, anti-tumoral cytotoxic T cells, M1-like macrophage, and dendritic cells increase in peritoneal cavity, and pro-tumoral regulatory T cells, M2-like macrophage decrease. In addition, neovascularization is inhibited resulting in reduction of ascites. However, since these multi-combination of immunotherapeutic agents have the potential to cause various immune-related adverse effects, many challenges remain to be resolved before they can be used clinically. In addition, it seems necessary to introduce various methods to enhance the patient's immunity in the process of cancer treatment.

## CONCLUSION

CRS with HIPEC is a treatment of choice for a carefully selected patients with CPM. CPM should be treated as both loco-regional and systemic disease in which a combination of surgical and medical therapies in synergy can improve the outcome of CPM patients. Future clinical trials are well underway ready to settle some of the heated debate regarding HIPEC.

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## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## AUTHOR'S CONTRIBUTIONS

Conceptualization: Woo Ram Kim. Data acquisition: Hye Jung Cho. Supervision: Woo Ram Kim. Writing—original draft: Hye Jung Cho. Writing—review & editing: Woo Ram Kim.

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