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Research Article

Theoretical Basis of Comprehensive Treatment for Colorectal Cancer Patients with Peritoneal Metastasis

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Abstract

The aim of this article is to describe the theory underlying Comprehensive Treatment (COMPT) designed to Cure Colorectal Cancer (CRC) patients with peritoneal metastasis (PM). There are four curative scenarios following COMPT. Scenario A involves cases without MM, where patients can potentially be cured by Complete Cytoreductive Surgery (CCRS) alone. Similarly, if the residual number of MM is below the threshold level that can be completely eliminated by intraoperative HIPEC(IOHIPEC). patients will be cured by CCRS plus IOHIPEC (Scenario C). If Neoadjuvant Chemotherapy (NAC) reduces the MM burden below the threshold level, patients may then be cured by CCRS combined with IOHIPEC (Scenario D). If NAC completely eliminates MM, patients will then be cured by CCRS alone (Scenario F). Cure is defined as survival without recurrence for longer than 5 years after following COMPT. The number of patients achieving a cure was 27/304 (8.9%), and the PCI was ≤ 12. Among 304 CRC-patients with PM who underwent CCRS, 10 patients treated with CCRS alone, and one patient with peritoneal cancer index (PCI) of 4 was cured (Scenario A). Three (20%) of 15 patients treated with CCRS plus IOHIPEC were cured. Four (5.5%) of 73 patients treated with NAC plus CCRS, were cured (Scenario F). Nineteen (9.2%) of 206 patients treated with CCRS plus HIPC after NAC were cured (Scenario C or D).

Conclusions: Patients with a PCI ≤ 12 could be cured with CCRS plus perioperative chemotherapy.

Keywords: Colorectal cancer; Peritoneal cancer index; Peritoneal metastasis; Peritonectomy

Introduction

Colorectal Cancer (CRC) is the second leading cause of cancer deaths. [1] Approximately 10% of CRC-patients die from Peritoneal Metastasis (PM) during treatment. [2] Standard treatments for CRC-patients with PM have consisted of systemic chemotherapy and palliative surgery. [3] However, these treatments cannot cure CRC with PM, and the median survival time after systemic chemotherapy alone was reported to be just 12.7 months [4]. Franko J et al. reported that all 364 CRC-patients with PM died of disease 8 years after systemic chemotherapy [4]. In the late 1990's, the Peritoneal Surface Oncology Group International (PSOGI) proposed an innovative treatment, Called Comprehensive Treatment (COMPT) [5]. It Combined Cytoreductive Surgery (CRS) and Perioperative Chemotherapy (POC). The aim of the COMPT is to cure patients with PM by combining CRS with POC to eradicate residual Micro Metastases (MM). During the last few decades, CRS combined with Intraoperative Hyperthermic Intraperitoneal Chemotherapy (IOHIPEC), has been used for resectable CRC-patient with PM. [6,7]. Verwaal VJ et al. reported on the efficacy of COMPT in CRC patients with PM, reporting longer overall survival (OS) and disease-free survival times than those who received standard surgical treatment and systemic chemotherapy. [8] Although post-operative mortality and morbidity after COMPT have been reported to be higher than with standard surgical treatment [9-11], COMPT is now being performed frequently. [12-14] The aim of the present study is to clarify the theory to underlying COMPT that has been designed to cure CRC patients with PM.

Patients and Methods

This retrospective study was conducted at two Japanese institutions, Kishiwada Tokushukai Hospital, and Ohmi General Hospital. Medical records of patients who underwent surgery for CRC-patients with PM between 2006 and 2022 were reviewed. The study protocol was approved by the Medical Ethics Committees of Kishiwada Tokushukai Hospital and Ohmi General Hospital (Protocol number; H19-2) and the ethics review board of each institution. Informed consent was obtained from all patients, who received this treatment. During the study periods, 945 CRC-patients with PM were treated with modern systemic chemotherapy, i.e., FOLFOX, FOLFIRI, SOX, IRIS, or CAPOX with or without bevacizumab or panitumumab. During systemic chemotherapy, 484 patients were selected as eligible to undergo complete cytoreduction using diagnostic imaging modalities. Cytoreduction was performed to resect all visible PM. [15-17] The peritoneal surface is divided into 13 sectors according to Sugarbaker et al. [15], and the sectors in which PMs were present are removed. However, sectors without macroscopic tumors are preserved.

Among 484 patients, Complete Cytoreductive Resection (CCRS) of PM could be performed in 356 (73.6%) patients. Just after CRS, HIPEC is performed using 4 L of saline heated to 42.5-43.5 ℃ for the duration of the IOHIPEC procedure (40 min). Therapeutic agents used in this procedure are oxaliplatin 300mg/person in the perfusate, with 500mg of 5-fluorouracil (5-FU) and 50 mg of levofolinate injected systemically 20 min. prior IOHIPEC. The thermal dose was calculated according to the method developed by Separeto and Dewey [18] and HIPEC is terminated when the thermal dose reaches 40 min.

Data Collection

Patients' data, perioperative chemotherapy, tumor histology, operative information and survival information were obtained from a prospectively maintained institutional database and also by chart review. The Peritoneal Cancer Index (PCI) was calculated as previously described by Jacquet et al. [19] Residual PM was evaluated using the Completeness Of Cytoreduction (CCR) score. [19] A score of CCR-0 indicates no visible PM, CCR-1 indicates the presence of residual macroscopic tumors. Overall survival was calculated as the time between the date of CRS and the date of death or the latest survival. Postoperative in-hospital mortality was defined as death due to any cause without discharge and within one month after CRS. Patients who survived for longer than 5 years after CRS or re-resection of recurrent tumors after first CRS were defined as cured patients [20].

Theory Underlying Curative Treatment of CRC-Patients with PM

In the treatment of CRC-PM, it is possible in some cases for cure to be achieved by surgery alone [21] (Figure 1). Nagata et al. reported that 2 of 7 patients with PM who underwent complete resection of PM were still alive without recurrence 5 years after CRS alone [21]. The PCIs of these patients were less than 2. In the treatment of PM from highly malignant tumor types like CRC, neither surgery alone nor chemotherapy alone can cure patients with PM. This is because CRC can metastasize not only on the peritoneal surface but also to other organs via hematogenous or lymphatic route. Patients treated with surgery alone will die due to the growth of residual Micrometastases (MMs), left after complete resection of macroscopic metastasis. Even in the case of a complete response to systemic chemotherapy, multi-drug resistant cancer cells remaining in the peritoneal cavity always regrow. Additionally, chemotherapy cannot be continued if severe side effects develop after several cycles of treatment. These outcomes are regarded as the treatment failures with chemotherapy.

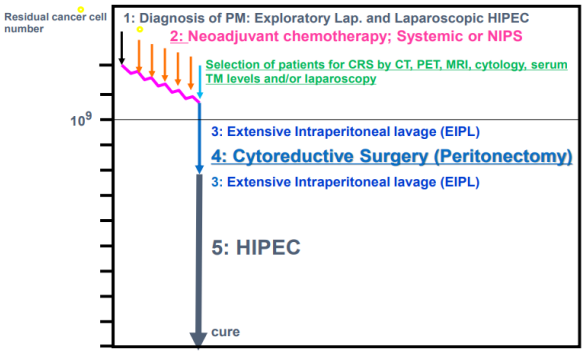

Figure 1: Time course relation between tumor burden (vertical bar) and treatment options used in comprehensive treatment.

Figure 1 shows the time-course relation between tumor burden and treatment options used in COMPT. As shown in Figure 1, neoadjuvant chemotherapy (NAC) is used to reduce MMs, some of which will remain on the preserved peritoneal surface, or outside the peritoneal cavity. PMs from CRC are usually treated with neoadjuvant systemic chemotherapy. Figure 2 shows the theoretical basis for curative treatment in patients with PM by COMPT. Scenario A shows without MM, meaning that the patients may often be cured by CRS alone. Because almost all CRC patients with PM have MM on the preserved peritoneal surface, patients cannot be cured by CCRS alone [11,17]. As shown in Scenario B without NAC, where patients are treated with CRS plus intraoperative HIPEC (IOHIPEC), in most cases, the patients will die after CCRS plus HIPEC due to the regrowth of MM. This is because the number of MM remaining after CCRS exceeds the limit of complete eradication for MM by IOHIPEC. In Scenario C without NAC where patients undergo CCRS plus IOHIPEC (Figure 2), most patients will be cured, since the residual number of MM remaining after CCRS is less than the threshold level that could be completely eliminated by IOHIPEC, In Scenario D where patients are treated with NAC plus CCRS plus IOHIPEC, most patients will be cured when the residual MM burden left after CCRS is less than the threshold level after NAC. However, when NAC cannot reduce the MM burden below the threshold level that can be completely eliminated by IOHIPEC, patients will die due to recurrence (Scenario E, Figure 2). If NAC completely eradicate MM, patients will be cured by CCRS alone (Scenario F). In trying to cure patients with PM, our aim is to induce patients to follow the treatment depicted in Scenario A, C, D, or F.

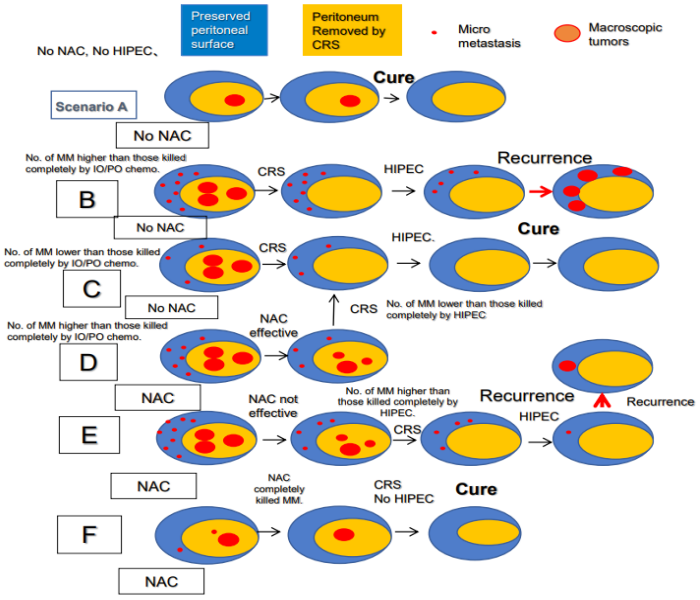

Figure 2: Theory underlying curative treatment of colorectal cancer-patients with peritoneal metastasis. Scenario A: No neoadjuvant chemotherapy and hyperthermic intraperitoneal chemoperfusion (IOHIPEC) (complete cytoreductive surgery alone). Scenario B and C: Complete cytoreductive surgery plus IOHIPEC without neoadjuvant chemotherapy, Scenario D, E, F: treated with neoadjuvant chemotherapy.

Statistical Analysis

All patients were followed and no patients were lost to follow-up. Outcome data were obtained from medical records and patients' interview. All statistical analyses were performed using SPSS software statistical computer package version 17 (SPSS Inc., Chicago, USA). The clinical variables were analyzed by X^2 tests and student T-test. Statistical significance was defined as a p-value ≤ 0.05. Survival times were estimated using Kaplan-Meier method, and survivals of each group of patients were compared with univariate analysis.

Results

Among 357 CRC-patients with PM who underwent CCRS (CCR-0 resection), 53 patients (6 died from other diseases and 47 patients surviving without recurrence within 5 years following CRS) were excluded, and 304 patients were analyzed to clarify

which treatments (NAC/IOHIPEC) contribute to cure. Among the 6 patients died from other diseases, five patients died from postoperative complications and 1 patient died from pancreatic cancer 7 years after CRS. All patients who underwent CCR-1 (incomplete CRS) died from their disease within 12.5 years after CRS and 5 year survival rate was 3.7%. Ten patients were treated with CCRS alone (Group I). Regarding the combination of NAC and IOHIPEC, 73 and 15 patients were treated with NAC plus CCRS without IOHIPEC (Group II) and with CCRS plus IOHIPEC without NAC (Group III), respectively. The number of patients treated with NAC plus CCRS and IOHIPEC was 206 (Group IV). Table 1 shows the PCIs of recurrent and cured patients. In Group I, 1 (10%) of 10 patients was cured, and the PCI of the cured patient was 4 in sector 6 and sector 10, and the histologic type was well differentiated adenocarinoma. In Group II, 4 (5.5%) of 73 patients were cured. The PCIs of the cured patients were 2, 4, 4, and 8 (4.5 ± 2.52), respectively, and those of recurrent patients in GROUP II was (9.30 ± 7.44, range; 1-28) (P=0.046). In Group III, the PCIs of cured patients were 2, 3, and 12 (5.67 ± 5.51, rage; 2-12), and those of recurrent patients was 7.87 ± 6.56, (range; 1-21) (NS).

	N	MST	5-year survial rate	10-year survial rate
CRS alone, Group I	10	1,08 Y	10%	NR
NAC plus CRS, Group II	73	2.21 Y	30.20%	11.70%
CRS plus IOHIPEC, Group III	15	2.70 Y	24.10%	24.10%
NAC plus CRS plus IOHIPEC, Group IV	206	2.32 Y	24.50%	12.00%

Table 1: Survival data of each Groups.

In Group IV, PCIs of cured patients and recurrent patients were 2. 84 ±2.03 (range; 1-8) and 8.41 ± 7.23 (range; 1-33), respectively (P<0.0001). Data of the survival rates of each group are shown in Table 1. There was a significant survival benefit in Group IV compared to Group I. The median survival (years) of Group I, II, III, and IV were 1.08, 2.21, 2.70, and 2.32 years, respectively. Additionally, the 5-year survival rates of each Group were 10.0%, 30.2%, 24.1%, and 24.5%, respectively. There was a significant survival benefit in Group IV compared to Group I (P=0.026, X2=4.929).

Discussion

The present study clearly demonstrated that the probability of achieving a cure is dependent on the residual MM burden after complete cytoreduction. In line with the PRODIGE 7 trial results, we also found that survival after CRS with or without IOHIPEC is related to the PCI levels [22]. Additionally, Sugarbaker PH and Elias D [5,7] reported that survivals after COMPT was closely associated with PCI, and that the higher the PCI, the worse the prognosis will be. The results indicate that the burden of MM after CCR-0 resection is related to the PCI score. According to our theory, cure depends on the MM burden after CCRS. When the MM burden after CCRS is less than the threshold levels that can be completely eradicated by IOHIPEC, patients will be cured. In contrast, if the MM burden exceeds the threshold level, patients will die to recurrence caused by the proliferation of residual cancer cells remaining after CRS plus IOHIPEC. In the treatment of CRC-patients with PM, CCRS alone can cure patients with a low PCI of less than 2 [21]. However, the cure rates by local resection using ordinary CRS technique alone were lower than 10% [21]. As demonstrated by PRODIGE-7 trial, 5-year survival rate of patients treated with the peritonectomy technique without intraoperative HIPEC was 36.7% (95% CI of median survival months: 35.1-49.7 months). Accordingly, extensive resection of peritoneal sectors with PM including greater omentum and peritoneum that tend to be affected by peritoneal free cancer cells [23,24], may improve the survival as compared with the ordinary local resection of peritoneum involved by PM. The reason for better survival after peritonectomy than after the standard resection of PM may be attributable to the simultaneous removal of micrometastasis around macroscopic tumors [17].

In the PRODIGE-7 study, all patients were treated by preoperative systemic chemotherapy, and would therefore belong to Scenario D, E, or F. The better survival in the PROGIGE-7 trial as compared with the survival after standard local resection is thought to be the effects of NAC resulting in a reduction of the MM left on the preserved peritoneal surface. In the PRODIGE-7 trial, PCIs were divided into three groups, i.e., ≤ 10, ≥ 11 and ≤15, and ≥16 and ≤25. The survival benefit obtained by IOHIPEC was found in the patients with PCIs ≥ 11 and ≤ 15. However, no improvement in survival was detected in the groups whose PCIs ≤ 10 and ≥ 16 and ≤ 25. Patients with PCIs of ≤ 10 may have a significantly lower MM burden than the other two groups, and some members of this group may belong to Scenario F under our theory. Consequently, it can be concluded that the survival was not improved by IOHIPEC. Patients with PCIs of ≥11 and ≤ 15 may be compatible with Scenario D, or E. and the MM burden may be reduced below the threshold level by NAC (Scenario D) .

Accordingly, IOHIPEC may have significantly improved survival in the PRODIGE-7 trial for the group whose PCI was 11 ≥ and 15≤. Patients with PCIs of ≥16 and ≤ 25 would equate in Scenario E under our theory. Subsequently, the prognosis of HIPEC and non-HIPEC group was not significantly different, because the residual MM left after CRS exceeded the threshold level, that can be completely eradicated by IOHIPEC.

In the present study, the number of patients cured was 27/304 (8.9%). Among 304 CRC-patients with PM, 10 patients treated with CCRS alone, and 1 patient with a PCI of 4 was cured (Scenario A). Three (20%) of 15 patients treated with CCRS plus IOHIPEC with a PCI of 2, 8, and 12 were cured. Seventy-three patients treated with NAC) plus CCRS, and 4 (5.5%) patients with PCIs of 2, 4, 4 and 8 were cured (Scenario F). Nineteen (9.2%) of 206 patients treated with CCRS plus HIPC after NAC were cured (Scenario C or D). The PCIs of the cured patients were 7.84 ± 2.03, range 1-8, Table 2). CRC-patients with a PCI ≤ 4 may be cured by CCRS alone. Patients with a PCI less than 12 could be cured with NAC plus complete cytoreduction plus IOHIPEC. The present results were obtained from a retrospective study, and need to be confirmed by conducting a prospective randomized study.

	CRS alone, Group I	NAC plus CRS, Group II	CRS plus IOHIPEC, Group III	NAC plus CRS plus IOHIPEC, Group IV
Recurrent patients	N=9	N=69	N=12	N=187
PCI (range)	1-24, (7.25 ± 6.35)	0-28, (9.30 ± 7.44)	1-21, (7.87 ± 6.56)	1-33, (8.41 ± 7.23)
Cured patients	N=1	N=4	N=3	N=19
PCI (range)	4	2, 4, 4, 8, (4.5 ± 2.52)	2, 3, 12, (5.67 ± 5.51)	1x7, 2x4, 3x2, 4x4, 6, 8 (2.84 ± 2.03)

Table 2: Peritoneal cancer index (PCIs) in recurrent and cured patients by comprehensive treatment.

Conclusions

CRC-patients with PM could be cured by COMPT. Among the options used in COMPT, complete cytoreduction plus IOHIPEC after NAC is the approach most likely to result in a cure. If more effective NAC or IOHIPEC to eradicate micrometastasis, prognosis of CRC-patients with PM will be radically improved.

We have to develop more powerful regimens of NAC and IOHIPEC.

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