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Research Article

A Comprehensive Treatment to Achieve Cure for Peritoneal Metastasis

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1. Abstract

This article aims to describe the rationale for comprehensive treatment (COMPT) in order to achieve cure of patients with peritoneal metastasis (PM).

1.1. Rationale of comprehensive treatment for cure in peritoneal metastasis

COMPT consists of complete resection of macroscopically detected PM and complete eradication of residual micrometastasis (MM) by intraoperative hyperthermic chemo-perfusion (HIPEC).

There are four possible scenarios for cure following COMPT. Scenario A involvs cases without MM, where patients will be cured by cytoreductive surgery (CRS) alone. Similarly, if the residual number of MM left after CRS is below than the threshold level that can be completely eliminated by intraoperative HIPEC, patients will be cured by CRS plus HIPEC (Scenario C).

If NAC reduces the MM burden below the threshold level, patients may then be cured by CRS combined with HIPEC (Scenario D). If NAC completely eliminates MM, patients will then be cured by CRS alone (Scenario F).

The number of patients cured of gastric cancer, colorectal and pseudomyxoma peritonei (PMP)-was 25/320 (7.8%) , 25/278 (9.0%), and 146/257 (56.8%), respectively.

Among patients with gastric cancer who had PM, all 21 treated with CRS alone died of recurrence, and no patients followed Scenario A. However, 8 (7.5%, in Scenario F) of 107 patients, 3 (8.3%, in Scenario C) of 36 patients and 14 (9%, in Scenario D) of 156 patients treated with CRS plus HIPEC after NAC were cured.

For colorectal cancer with PM, 1 (11.1%, in Scenario A) of 9 patients,2 (3.3%, in Scenario F) of 60 patients treated with NAC plus CRS without HIPEC were cured. Three (21.4%, in Scenario C) of 14 patients treated with CRS plus HIPEC without NAC were cured. Additionally, 19 (9.7%, in Scenario D) of 195 patients treated with CRS plus HIPEC after NAC were cured.

Among PMP patients, 17 (40.5%, in Scenario A) of 42 patients treated with CRS alone were cured. Six (28.5%, in Scenario F) of 21 patients treated with CRS without HIPEC after NAC were cured. In contrast, 75 (71.4%, in Scenario C) of 105 patients treated with CRS plus HIPEC without NAC, and 48 (52.9%, in Scenario D) of 89 patients treated with CRS plus HIPEC after NAC were cured.

1.2. Conclusions: The present study primarily demonstrated the mechanisms by which cured can be achieved with PM from gastric cancer, colorectal cancer, and PMP. Mechanisms of cure are different from disease to disease. HIPEC may completely eradicate MM left after CRS, and NAC may reduce the MM burden. Patients with PM should be treated with NAC to reduce PCIs and MM. When the patients treated using NAC are considered able to undergo complete, CRS, CRS and intraoperative HIPEC are recommended.

2. Keywords: Peritoneal metastasis; Gastric cancer; Colorectal cancer; Mesothelioma; Pseudomyxoma peritonei; HIPEC; Peritonecto-

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my; Peritoneal cancer index

3. Introduction

In the early 1990s, peritoneal metastasis (PM) were considered an incurable condition, when treated using systemic chemotherapy or surgery alone [1]. In 1999, Peritoneal Surface Oncology Group International (PSOGI) proposed a novel treatment named comprehensive treatment (COMPT) that combined cytoreductive surgery (CRS) and perioperative chemotherapy (POC) [2-4]. Cure could be achieved with a combination of complete removal of macroscopic tumors by peritonectomy and complete eradication of micrometastasis (MM) left after peritonectomy by POC [1]. POC comprises neoadjuvant chemotherapy (NAC), intraoperative hyperthermic peritoneal chemotherapy (HIPEC), and postoperative chemotherapy (POC). Among these forms of chemotherapies, intraoperative HIPEC may have an important role in the complete elimination of MM, because the tumor burden is least just after CRS. Chemotherapeutic agents used in HIPEC can kill proportion of cancer cells at specific points in the cell cycle, but hyperthermia at temperatures over 43 Celsius intduces irreversible damage to cancer cells in a time-dependent manner without relation to the cell cycle [5].

This article intends to describe the rationale for COMPT in achieving cure of patients with PM, as well as the utility of HIPEC in its effect on the peritoneal cancer index (PCI) and peritoneal cytologic status. Additionally, the roles of NAC, CRS, and HIPEC will be presented.

4. Rationale of Comprehensive Treatment for Cure in Peritoneal Metastasis

In the treatment of PM from colorectal cancer and pseudomyxoma peritonei, cure might be achieved by surgery alone [6,7] (Figure 1). Nagata et al. reported that 2 of 7 colorectal cancer-patients with PM who underwent complete resection were still alive without recurrence five years after CRS alone. PCIs of the patients were less than [2,6].

In the treatment of PM from cancers with highly malignant behavior like gastric cancer, neither surgery nor chemotherapy alone can cure patients with PM. Patients treated with surgery alone will die due to the growth of residual MM left after complete resection of macroscopic metastasis [3]. Even in complete responders to systemic chemotherapy, multi-drug resistant cancer cells contaminate in the PM always regrow, and consequently systemic chemotherapy will fail. Additionally, chemotherapy cannot be continued due to the development of severe side effects after several cycles. These factors are considered to account for treatment failure with chemotherapy.

Figure 1 shows the relationship between tumor burden (vertical line) and treatment options used COMPT. NAC is used to reduce MM burden, which will be left on the peritoneal surface after CRS, or outside the peritoneal cavity in the liver or lung. PM from colorectal cancer are usually treated with neoadjuvant systemic chemotherapy. In contrast, neoadjuvant intraperitoneal/systemic chemotherapy (NIPS) is more effective for PM from gastric cancer, ovarian cancer and pseudomyxoma peritonei, than systemic chemotherapy [8-10].

After 6 cycles of NIPS or systemic chemotherapy, candidates for CRS are selected by laparoscopy, computed tomography (CT), Magnetic Resonance Imaging (MRI), and/or Positron Emission Tomography (PET).

At laparotomy, peritoneal cytology is performed, and intraoperative extensive intraperitoneal peritoneal lavage using 10 liter of saline is performed to remove free cancer cells from peritoneal cabity, and likewise mucinous materials containing tumor cells of pseudomyxoma peritonei [11]. Next, the peritoneal cancer index (PCI) is counted, and curability is determined [2,4]. If the small bowel and its mesentery are diffusely involved, complete cytoreduction cannot be performed. Additionally, patients with PCI values that exceed the threshold levels are excluded from consideration for CRS. Threshold levels of PCI are established because above these levels are sighificantly wirse, even after complete cytoreduction.

PCI threshold values differ from disease to disease, and those for gastric, colorectal cancer, and pseudomyxoma peritonei are 12, 21, and 28, respectively [7].

In CRS, primary tumors and regional lymph nodes are removed in combination with the removal of peritoneal sectors involved by PM using peritonectomy technique [2]. When the PM was detected on one sector, the involved sector is removed with macroscopic PM to remove invisible MM around the macroscopic PM. The final aim of surgeons is to remove all the macroscopic tumors, resulting in complete cytoreduction (CCR-0). When the CRS is incomplete, prognoses of patients after CRS will be dismal [2,7].

Figure 2 shows the theoretical basis of the treatment of PM by COMPT. Scenaria A shows without MM, where patients will be cured by CRS alone.. As shown in Senario B without NAC, all patients will die after CRS + HIPEC due to the regrowth of MM, because the number of the MM left after CRS exceed the limit of complete eradication by intraoperative HIPEC.

WithScenario C (Figure 2), however, if the residual number of MM left after CRS is less than the threshold level that could be completely eliminated by intraoperative HIPEC, patients will be cured.

When the residual MM burden left after NAC and CRS exceeds the threshold level that can be completely eliminated by HIPEC, patients will die of recurrent disease after NAC+CRS+HIPEC. However, when NAC reduce the MM burden below the threshold level that can be completely eliminated by HIPEC, patients might be cured by intraoperative HIPEC (Scenario D). In contrast, if NAC fail to reduce the number of MM below the threshold levels, patients will die of recurrent disease (Figure 2, Scenario E).

As shown in Scenario F, when NAC completely eliminates MM, patients will be cured by CRS alone.

In trying to cure patients with PM, our aim is to induce patients to follow Scenario A, C, D, or F.

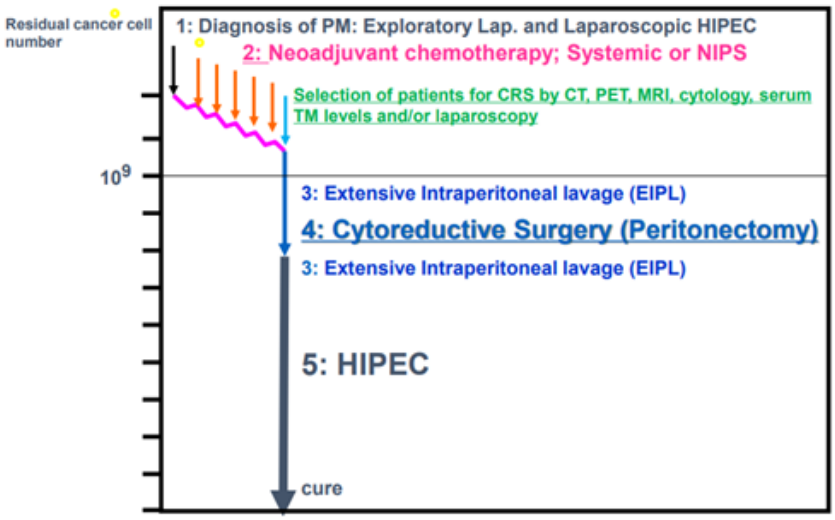

Figure 1: Tumor burden (vertical bar) and treatment options used in a comprehensive treatment

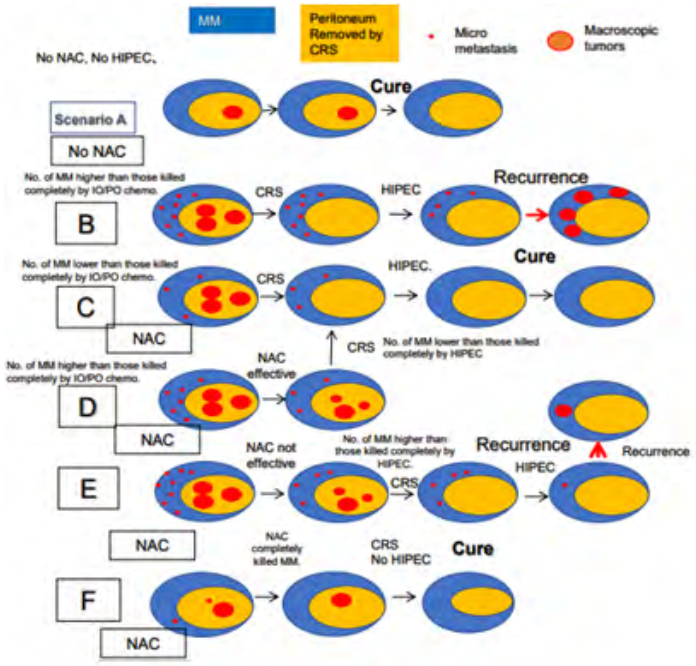

Figure 2: Rationale to achieve cure of patients with peritoneal metastasis by COMPT

5. Effects of laparoscopic HIPEC on peritoneal cancer index

To evaluate the direct effect of HIPEC, laparoscopic HIPEC (LHIPEC) was performed [12].

After observation of the peritoneal surface and determination of PCI by laparoscopy, the peritoneal cavity is perfused for 60 min with 4000ml of saline heated at 43 to 43.5 °C, containing 40mg each of docetaxel and cisplatin was performed in 56 patients with PM from gastric cancer.

In 32 colorectal cancer and 83 pseudomyxoma peritonei (PMP) from an appendiceal mucinous neoplasm (AMN), 500mg of 5-fluorouracil and 50 mg of isovorin in 50 ml of saline were injected intravenously and HIPEC was performed with 300mg of oxaliplatin, mixed in the 4000 ml of heated saline. During HIPEC, temperature of peritoneal cavity was monitored by two thermal sensors, placed on the undersurface of the diaphragm and pelvis. HIPEC was completed when the thermal doses of the monitored area reached 40 min [5]. One month after LHIPEC, a second laparoscopic examination was done, and PCI and cytologic changes were compared with the PCI and cytologic status at the first LHIPEC.

6. Patients treated based on the rationale of comprehensive treatment

Complete cytoreduction and NAC and/or HIPEC carried out based on the concept of COMPT (Figure 1) was performed in 610, 475, and 720 patients respectively with gastric cancer, colorectal cancer, or pseudomyxoma peritonei from low grade mucinous neoplasm from the appendix. Among these patients, macroscopic complete cytoreduction could be performed in 320, 278 and 257 patients, respectively. Postoperative survivals and recurrence were analyzed

according to the treatment modalities. Patients who survived without recurrence longer than five years after COMPT were defined as cured [13].

7. Statistical Analysis

All patients were followed and no patients were lost to follow-up. Outcome data were obtained from medical records and patient interviews. All statistical analyses were performed using SPSS software statistical computer package version 17 (SPSS Inc., Chicago, USA). The clinical variables were analyzed by Chisquared tests and Student's-test. Statistical significance was defined as a p-value ≤0.05. Survival times were estimated using the Kaplan-Meier method, and survivals of each group of patients were compared using univariate analysis.

8. Results

8.1. Changes in PCI after one cycle of LHIPEC (Table 1)

After one cycle of LHIPEC, PCIs in gastric cancer were significantly reduced by 1.8 from 13.3 ± 11.0 to 11.5± 10.6 (P=0.021, N=56). PCIs before LHIPEC in pseudomyxoma peritonei, were 11.2 ± 9.5, and those one month after LHIPEC were 8.2± 9.8. There was a significant reduction in PCI one month after LHIPEC (P=0.0009, N=83).

However, the PCI of colorectal cancer (N=32) before LHIPEC was 10.7 ± 8.4, but one month after LHIPEC it was 13.2± 10.3 (P=0.057). No significant difference was found in PCIs between before and after LHIPEC.

With gastric cancer, positive cytology at LHIPEC was found in 26 of 47 (55.3%) and 19 (40.4%) of 47 patients at one month after LHIPEC (P<0.05), Fifteen (57.6%) of 26 patients showing positive cytology at first LHIPEC develpoed negative cytology one month after LHIPEC. In colorectal cancer, cytology was positive in 14 (66.7%) and 9 (42.5%) of 21 patients before and after LHIPEC, respectively. Six (42.9%) of 14 patients who had positive cytology before LHIPEC became negative after LHIPEC. In PMP patients, 50 (60.9%) and 31 (37.1%) of 83 patients showed positive cytology before and after LHIPEC, respectively (P<0.05). After LHIPEC, 22 (44.0%) of 50 patients with positive cytology at the first LHIPEC became to be negative after LHIPEC.

Table 1: PCI changes after one cycle of laparoscopic HIPEC.

	PCI before LHIPEC	PCI one month after LHIPEC	P
gastric cancer N=56	13.3 ±11.0	11.5 ±10.6	P=0.0213
colorectal cancer N=32	10.7 ± 8.4	13.2 ± 10.3	P=0.057
Pseudomyxoma peritonei (N=83)	11.2 ± 9.5	8.2 ± 9.8	P=0.0009

8.2. Survival analysis and cured patients after COMPT

Median survival time (MST) of patients with PM from gastric, and cotal canclorecer were 19.2 and 43.6 months, respectively, and five-year survival rates of patients with PM from gastric cancer, colorectal cancer and PMP were 14.2%, 33.6%, and 80.0%, respectively. Ten-year survival rates were 9.3%, 14.6% and 72.2%, respectively.

The number of patients cured of gastric cancer, colorectal cancer and PMP was 25 /320 (7.8%) , 25/278 (9.0%), and 146/257 (56.8%) patients (Table 2).

Among patients with gastric cancer patients who had PM, all 21 treated with CRS alone died of recurrence, and no patients folloed Senario A (Figure 2). However, 8 (7.5%, in Scenerio F) of 107 patients treated with NAC plus CRS without HIPEC were cured. Additionally, 3 (8.3%, in Scenario C) of 36 patients treated with CRS plus HIPEC without NAC were cured, and 14 (9%, in Scenario D) of 156 patients treated with CRS plus HIPEC after NAC were cured.

In colorectal cancer with PM, 1 (11.1%, in ScenarioA) of 9 patients treated with CRS alone was cured, and 2 (3.3%, in Scenario F) of 60 patients treated with NAC plus CRS without HIPEC were cured. Three (21.4%, in Scenario C) of 14 patients treated with CRS plus HIPEC without NAC were cured. Additionally, 19 (9.7%, in Course Scenario D) of 195 patients treated with CRS plus HIPEC after NAC were cured.

In PMP patients, 17 (40.5%, in Scenario A) of 42 patients treated with CRS alone were cured. Six (28.5%, in Scenario F) of 21 patients treated with CRS without HIPEC after NAC were cured. In contrast, 75 (71.4%, in Scenario C) of 105 patients treated with CRS plus HIPEC without NAC, and 48 (52.9%, in Scenario D) of 89 patients treated with CRS plus HIPEC after NAC were cured, respectively.

In gastric cancer, Scenario A, B, C, D, E and F comprised 0 (0%), 33 (10.3%), 3 (0.9%), 3 (0.9%), 14 (4.4%), 142 (44.4%) and 8 (2.5%) of cases, respectively, for colorectal cancer with PM the resective numbers were 1 (0.4%), 11 (4.0%), 3 (1.1%), 19 (6.8%), 176 (63.3%) and 2 (0.7%).

For PMP, the corresponding numbers were 17 (6.6%), 30 (11.7%), 75 (29.2%,) 48 (18.7%), 41 (16.0%), and 6 (2.3%).

After CRS alone, the cure rate (17/42; 40.4%) in PMP patients was significantly higher than that for gastric and colorectal cancer patients with PM (1/30; 3.3%) (P=0.0002).

Five-year survival rates after CRS alone, NAC+CRS without HIPEC, NAC+CRS +HIPEC, and CRS +HIPEC without NAC in gastric cancer were 4.8%,11.2%, 13.5%, and 17.2%, respectively, and the survival after CRS alone was significantly poorer than that inpatients treated with CRS plus/minus NAC or HIPEC. In colorectal cancer with PM, five-year survival rates with CRS alone, NAC plus CRS without HIPEC, NAC plus CRS with HIPEC, and CRS plus

HIPEC without NAC were 13.3%, 31.9%, 22.9%, and 25.0%, respectively. There was no survival difference between each group.

The corresponding values for PMP were 84.8%, 81.5%, 92.1%, and 90.6%, respectively.

8.3. Postoperative morbidities and mortalities

Grade 3 postoperative complications after CRS of gastric cancer, colorectal cancerand PMP patients occurred in 11.8%, 7.4%, and 9.8%, respectively. Grade 4 complications were experienced in 7.6%, 9.7% and 8.7%, respectively. Grade 5 mortality of each disease were 0.8%, 1.0% and 1.1%, respectively (Table 3).

Table 2: Patients who survived longer than 5 years without recurrence after comprehensive treatment.

	No NAC and no HIPEC; Course A	NAC without HIPEC (Course F)	HIPEC without NAC Course B/C	HIPEC+NAC (Course Course D/E)	Total (cure rates)
Gastric cancer	0/21 (0%)	8/107 (7.5%)	3/36 (8.3%)	14/156 (9.0%)	25/320 (7.8%)
Colorectal cancer	1/9 (11.1%)	2/60 (3.3%)	3/14 (21.4%)	19/195 (9.'%)	25/278 (9.0%)
Pseudomyxoma peritonei	17/42 (40.5%)	6/21 (28.5%)	75/105 (71.4%)	48/89 (52.9%)	146/257 (56.8%)

Table 3: Survivals of patients with peritoneal metastasis, who received complete cytoreduction according to the treatment modalities.

Gastric cancer	N	MST (months)	5-year survivasl rate	10-year survival rate	P
No NAC and no HIPEC	21	10.9	4.80%	0%	0.0001
NAC without HIPEC	107	20	11.20%	10.00%	
NAC with HIPEC	156	20.5	17.20%	9.40%	
HIPEC without NAC	36	15.8	13.50%	NR	
Colorectal cancer					
No NAC and no HIPEC	9	13.2	13.30%	NR	NS
NAC without HIPEC	60	26	31.90%	10.60%	
NAC with HIPEC	195	28.7	25.9	12.70%	
HIPEC without NAC	14	18	22.90%	22.90%	
Pseudomyxoma peritonei, Low grade					
No NAC and no HIPEC	42	NR	84.80%	69.50%	NS
NAC without HIPEC	21	94.8	81.50%	49.40%	
NAC with HIPEC	89	NR	90.60%	86.10%	
HIPEC without NAC	105	NR	92.10%	87.30%	

9. Discussion

COMPT is the only method hat can provide a cure in patients with PM, and is now performed as standard treatment of PM in colorectal cancer [14,15]. The rationale behind COMPT for the cure of PM is elimination of MM left after complete macroscopic resection of PM. As shown in Figure 2, cure is achieved using COMPT in patients who follow Scenario A, C, D and F.

At present, chemotherapy cannot achieve complete eradication of macroscopic tumors. In contrast, MM can be completely eliminated by several cycles of chemotherapy. The main aim of NAC is to reduce residual MM on the peritoneal surface, following CRS. Anti-cancer drugs are known to have the potential to kill a certain fraction of cancer cells depending on where they are in the cell cycle. Accordingly, repeat treatment by chemotherapy is essential to achieve reduction of MM. In this sense, NAC was performed for six cycles, because tumors may become chemo-resistance after more than 7 cycles [7].

In gastric cancer, the cure rate after CRS alone was 0% (0/21). In contrast, cure rates after CRS plus NAC with or without HIPEC and after CRS plus HIPEC with or without NAC were 8.3% (22/263), and 8.6% (17/192), respectively. In addition, cure rate after CRS plus HIPEC and NAC was 14/156 (9.0%). Accordingly, NAC or HIPEC is essential to achieve cure in yreating gastric cancer.

In colorectal cancer, cure rate after CRS alone was 11.1% (1/9). Cure rates after CRS plus NAC with or without HIPEC and after CRS plus HIPEC with or without NAC were 8.3% (21/255), and 10.5% (22/209), respectively. In addition, cure rate after CRS plus HIPEC and NAC was 22/209 (10.5%). That of patients treated with CRS plus NAC plus HIPEC was 9.7% (19/195). In PMP, cure rate after CRS alone was 40.5% (17/42). Cure rates after CRS plus NAC

with or without HIPEC and after CRS plus HIPEC with or without NAC were 49.1% (54/110), and 63.4% (123/194), respectively. Cure rate after CRS plus NAC and HIPEC was 52.9% (48/89). These results indicate that NAC or HIPEC is not always necessary for cure in colorectal cancer-patients with PM and PMP-patients.

One cycle of intraoperative chemotherapy cannot achieve total cell kill of MM, because of the limitation of the mechanisms by which chemotherapy kills cells [7].

In COMPT, intraoperative HIPEC is used for the eradication of MM.

Hyperthermia above 43 Celsius introduce irreversible changes in cancer cells, and cancer cells die exponentially in a time-dependent manners [5]. According to an in vitro study by Sapareto SA, hyperthermia above 43.5 Celsius alone for 60 minutes kills 99% of cells [5]. Additionally, hyperthermia enhances cell kill when combined with some anti-cancer drugs [17,18].

During the treatment using COMPT, the residual cancer cell burden is least just after complete cytoreduction. Accordingly, complete eradication of MM may be achieved by intraoperative HIPEC.

If the burden of residual MM is less than the threshold level, that allows complete killing with one cycle of HIPEC, patients may be cured by CRS plus HIPEC. As shown in our study, PCIs of gastric cancer and PMP were significantly reduced after one cycle of LHIPEC. However, LHIPEC did not reduce PCI of PM from colorectal cancer. This may be due to a dependency on the size the size of PM, because PM from colorectal cancer are larger than 2 mm in diameter. The diffusion distance of heat limits its effect to within 2 mm of the pitoneal surface [16].

In addition, positive cytology became negative after LHIPEC for gastric cancer, colorectal cancer and PMP. Thus. HIPEC was shown to be effective in reducing PCI scores in gastric cancer and PMP, and to eradicate peritoneal free cancer cells in gastric cancer, colorectal cancer, and PMP.

The present study also demonstrated cures of gastric cancer following CRS without HIPEC with or without NAC, and following CRS plus HIPEC with or without NAC with rate of 8/128 (6.3%) and 17/192 (7.3%) (NS). Those of colorectal cancer were 3/69 (4.3%), and 22/209 (10.5%), respectively.

For PMP, these were 23/63 (36.5%), and 123/194 (63.4%), (P-0.0086, X2=4.67). These results indicate that intraoperative HIPEC significantly increased the cure rate of PMP patients.

Kusamura et al. reported that HIPEC was associated with better overall survival when performed after CRS in patients with PMP, generally without adverse effects on surgical outcomes in the cohort study analyzed data from the Peritoneal Surface Oncology Group International (PSOGI) registry, including 1924 patients with histologically confirmed PMP due to an appendiceal mucinous neoplasm. . .

Complications after CRS were similar to those after pancreatoduodenectomy or esophagectomy, and the rates were considered as an acceptable levels.

10. Conclusions

The present study primarily demonstrates cure of PM from gastric cancer, colorectal cancer, and PMP. HIPEC may completely eradicate MM left after CRS, and NAC may reduce the MM burden. Patients with PM should be treated with NAC to reduce PCIs and MM. After NAC, eligibility for CRS must be determined by PET, MRI and CT. When the patients treated with NAC are assessed as suitable to receive complete CRS, CRS and intraoperative HIPEC are recommended. Our results were obtained from retrospective study. These should be confirmed by prospective studies.

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