Original Article

Feasibility of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) for Patients with Peritoneal Carcinomatosis from Colorectal Cancerin Short-term Outcome

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Key Words
Peritoneal carcinomatosis;
Intraperitoneal chemotherapy

Purpose. Cytoreductive surgery combined with intraperitoneal chemotherapy has been used to treat colorectal cancer with peritoneal carcinomatosis. In this study, we assessed the short-term surgical outcomes of hyperthermic intraperitoneal chemotherapy.
Methods. Twenty-two patients with peritoneal cancer metastasis who were receiving HIPEC therapy were included in this study. A cytoreductive procedure was performed before HIPEC therapy for most patients. In addition, we used a closed system with FOLFOX or irinotecan + oxaliplatin as a chemotherapy regimen for at least 1 hour.
Results. The mean age of patients was 59.59 ± 10.99 years, and their mean peritoneal cancer index was 10.27 ± 6.06. Eighteen of the twenty-two patients received a cytoreductive procedure. During the follow-up period, 5/22 (22.7%) patients died because of disease progression. The complications included enterocutaneous fistula (13.6%), anastomosis leakage (9.1%), pleural effusion (9.1%), ureteral stricture (4.5%), and entero-vesicle fistula (4.5%).
Conclusions. The complication rate of hyperthermic intraoperative chemotherapy therapy was acceptable to the patients with peritoneal metastasis.
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According to the Health Promotion Administration in Taiwan, 15,140 patients have been newly diagnosed as having colorectal cancer (CRC), and 5,265 deaths have occurred annually from the disease in 2013.[1] A total of 30%-40% of patients with CRC have a locally advanced disease (stages II-III), and ~20% have distant metastasis (stage IV).[2,3] Peritoneal carcinomatosis is discovered in ~5%-10% of patients during the primary surgery,[4] and 20%-50% of patients with recurrence may receive a curative intent procedure because of metastasis restricted to the peritoneal cavity.

Traditional systemic chemotherapy for CRC with peritoneal metastasis is associated with a median survival time of 5-7 months.[4] Even when traditional chemotherapy is combined with target therapy, the overall survival time has been shown to be prolonged only by 3-5 months.[5,6] This limited improvement is proba-

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bly because the peritoneum-plasma barrier prevents chemotherapeutic drugs from entering the systemic circulation within the peritoneal cavity.[7] Dedirck et al. proposed intraperitoneal chemotherapy in 1978 with the goal of achieving a higher drug concentration and longer half-life in the peritoneal cavity.[8] In 1980, Spratt first described the combination of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC).[9]

In Taiwan, there have been few reports to date that have provided intraperitonal chemotherapeutic results. In this study, we reviewed our cases treated at the National Taiwan University Hospital to collect data on postoperative complications and survival times.

Patients and Methods

For this study, we selected consecutive patients (from July 2015 to April 2016) with highly suspected intraperitoneal cancer metastases detected by preoperative, multislice, spiral computed tomography, positron emission tomography, or intraoperative vision. The patients selected to be treated with curative intent underwent the surgical procedure of cytoreduction followed by HIPEC therapy. If the intra-abdominal organ exhibited severe cancer seeding, a palliative procedure with HIPEC was also considered. We used a peritoneal cancer index[24] system for scoring (Fig. 1).

The surgical procedures were similar to exploratory laparotomy. After making a long mid-line surgical opening in the abdominal cavity, we checked the omentum, diaphragm and liver surface, pelvic cavity, mesentery and bowel serosa, and peritoneal condition. If the condition allowed us to perform at least R1 resection, then cytoreduction was performed followed by HIPEC therapy. If cytoreduction could not achieve R1 resection, a debulking or palliative surgical procedure was performed followed by HIPEC therapy.

The regimen we used for hyperthermic intraperitoneal chemotherapy was fluorouracil 1500 mg/m^2 plus leucovorin calcium 170 mg/m^2 in 0.9% normal saline solution 250 ml, and oxaliplatin 85 mg/m^2 in 5% dextrose solution. After placement of drains to allow solutions to be pumped in and out, the abdominal wound was closed first. Sodium chloride solution (2000-4000 ml) was injected before administering the chemotherapeutic solution so that every organ surface would be contacted by the chemotherapeutic solution.

The temperature was set to 42 °C, and the machine monitored the inflow and outflow temperature to maintain the proper temperature in the abdomen. After 1 hour of intraperitoneal chemotherapy, the chemotherapeutic solution was pumped out, and 1000 ml of sodium chloride was injected to wash out any residual drug. The drains were left in place for further use but were removed after the amount of ascites decreased.

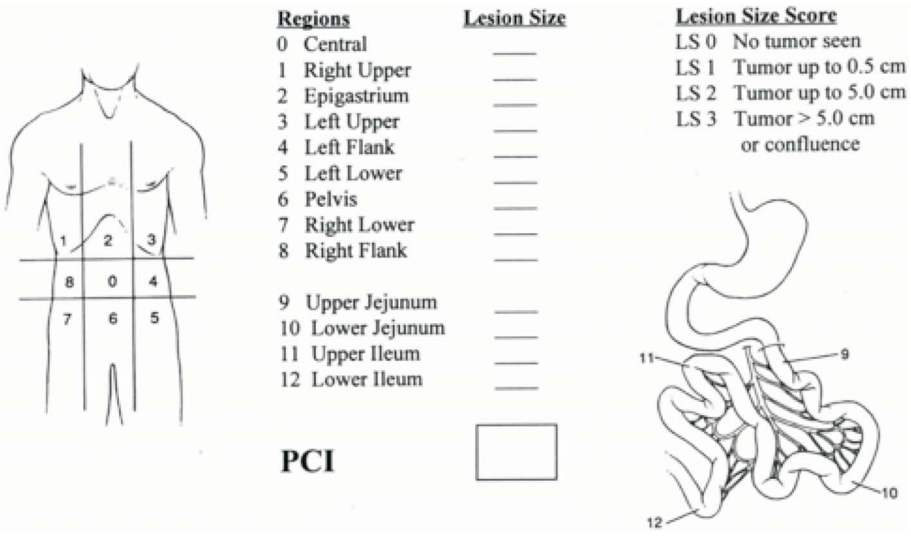

Fig. 1. Peritoneal cancer index.

Results

Between July 2015 and April 2016, a total of 26 patients received intraperitoneal chemotherapy in our institution. Of these patients, four did not receive hyperthermic control during chemotherapy. The other 22 patients all underwent complete hyperthermic intraperitoneal chemotherapy (HIPEC). The patients were followed to review their conditions for at least 60 days and until June 2016.

There were 11 male and 11 female patients included in this study (Table 1). Five of the patients were first diagnosed as having colon cancer with intraperitoneal metastasis, and the remaining 17 patients had had previous surgical intervention but cancer recurrence had been noted during the follow-up period. The mean age of the patients was 59.59 ± 10.99 years, and the primary cancer types were ascending cancer (n = 7), descending colon cancer (n = 3), sigmoid colon cancer (n = 6), rectal cancer (n = 5) (including 1 patient who also had ovarian cancer), and endometrial cancer (n = 1). The mean peritoneal cancer index of the patients was 10.27 ± 6.06.

All of the patients received FOLFOX intraperitoneal chemotherapy for at least 1 h except for one female patient who experienced hypotension during the HIPEC period; a suspected hyperthermic condition caused vasodilation and hypotension. Eighteen patients underwent cytoreduction before HIPEC; three of them achieved R0 resection and 13 achieved R1 resection. Four patients only received palliative treatment.

For the patients who underwent intensively curative procedures, all of the invasive cancer area was resected to achieve at least R1 resection. The intraoperative complications are presented in Table 2. Four of the patients received radio frequency therapy for liver metastasis. Most of the patients were transferred to the intensive care unit after the procedure. However, if a patient had undergone a relatively non-

Table 1. Clinical data of the patients who received HIPEC therapy

Age (years)	Sex	Primary cancer	Time to recurrence (month)	PCI[a]	Resection margin	Resect organ
61	M	Cecal cancer	39	21	R2	Nil
79	M	Cecal cancer	31	10	R1	Partial stomach, A-colon
60	M	D-colon cancer	5	19	R2	Peritoneum
61	F	Cecal cancer	1	19	R2	Peritoneum
68	M	S-colon cancer	22	15	R1	Omentum, ileum
60	F	Cecal cancer	5	10	R1	Peritoneum, small bowel, diaphragm, liver RFA
54	F	Endometrial cancer	37	5	R1	Peritoneum, ileum, rectum
47	F	D-colon cancer	First diagnosis	5	R1	D-colon, kidney, small bowel
72	M	S-colon cancer	First diagnosis	18	R1	Colon, ureter
42	F	S-colon cancer	34	8	R1	Peritoneum, small bowel
68	M	Rectal cancer	6	1	R0	Rectum, small bowel
77	M	S-colon cancer	48	10	R1	Omentum, peritoneum
63	F	Cecal cancer	5	2	R0	Peritonuem, previous right hemicolectomy anastomosis site
60	M	S-colon cancer	10	12	R1	Peritoneum, omentum, small bowel, rectum, ureter
65	F	Rectal cancer	6	10	R1	Peritoneum, small bowel, omentum, ureter
60	M	D-colon cancer	14	15	R1	Peritomeum, A-colon
72	F	S-colon cancer	First diagnosis	5	R0	Sigmoid colon, bladder, uterus, small bowel
60	F	Ovarian cancer & rectal cancer	First diagnosis	8	R2	Ovary, omentum
49	F	Rectal cancer	17	7	R1	Peritoneum, ovary, uterus, ureter, bladder
45	M	Cecal cancer	First diagnosis	4	R1	A-colon
39	M	S-colon cancer	5	18	R2	Small bowel, peritoneum
49	F	Cecal cancer	2	4	R2	Omentum, peritoneum

[a] PCI: peritoneal cancer index.

invasive procedure and their postoperative condition was stable, the patient was extubated and sent back to the ordinary care ward. The mean duration in the intensive care unit was 3.2 days, but a 68-year-old male patient insisted on staying in the ward at his own expense and remained for 359 days. The mean inpatient stay was 28.95 ± 19.25 days. Short-term survival was defined as more than 6 months, and the short-term survival rate was 54.5%.

As of June 30, 2016, five of the patients had expired after HIPEC treatment (Table 3). Surgical mortality was defined as death within 1 month after the procedure, and the surgical mortality rate was 4.5%. The remaining patients received chemotherapy plus target therapy. The survival time was 180.13 days ± 84.39 days. Postoperative complications included enterocutaneous fistula (13.6%), anastomosis site leakage (9.1%), pleural effusion (9.1%), ureteral stricture (4.5%), and entero-vesicle fistula (4.5%) (Table 4).

Discussion

Treatment of peritoneal metastasis of colorectal or other cancersis a significant challenge, either at initial presentation or recurrence. However, with traditional systemic chemotherapy, only 4% of patients live for 5 years.[10] Cytoreductive surgery of peritoneal metastasis is another option that may prolong survival. Some studies[11-14] have shown a median survival time of approximately 25-30 months for cytoreductive surgery without intraperitoneal chemotherapy. This survival is similar to that for patients who undergo laparotomy but with no resection or chemotherapy; their median survival time was 25 months.[13] Therefore, intraperitoneal chemotherapy after cytoreductive surgery is necessary.

Complications are the primary concern after intraperitoneal chemotherapy. According to review articles, the most common complication is wound infection or dehiscence, which occurs in 3%-12% of patients.[16-22] The second most common complicationis fistula, which occurs in 1% to 11% of patients.[17-22] In our study, anastomosis site leakages were noted in 3 patients (13.6%). In 1 patient, cancer had invaded the pylorus region and was treated by resection and pylorus repair. Leakage at the repair site was detected by the presence of gastric juice in the drain tube, so the patient underwent re-operation for repair with jejunostomy for feeding. The second patient received palliative feeding jejunostomy and adhesiolysis. During the

Table 4. Complications after HIPEC therapy

	Within 60 days	During the follow-up period
Leakage	3 (13.6%)	3 (13.6%)
Pleural effusion	2 (9.1%)	2 (9.1%)
Fistula	2 (9.1%)	3 (13.6%)
Intra-abdominal abscess	1 (4.5%)	1 (4.5%)
Ureteral stricture	0	1 (4.5%)

Table 2. Complications during the operation

	Case number	Reason
Diaphragm perforation	1 (4.5%)	Tumor seeding on the diaphragm
Urinary bladder perforation	2 (9.1%)	Tumor direct invaded to the bladder
Ureteral re-anastomosis or reconstruction	4 (18%)	Injury while removed the para-ureteral soft tissue
Nephrectomy	1 (4.5%)	Gerota fascia was invaded by tumor

Table 3. Clinical data of the patients who died after HIPEC therapy

Age	Sex	Procedure	Complications	Survival period (day)
61	M	jejunostomy + HIPEC	Ileus, aspiration pneumonia	89
79	M	colectomy + pylorus resection + HIPEC	Pylorus leakage	161
60	M	bypass + HIPEC	ARDS with ventilator support	132
61	F	feeding jejunostomy + HIPEC	ARDS	9
68	M	right hemicolectomy + HIPEC	Ileus, vesicle-rectal fistula	196

procedure, we noted some seeding tumor at the bowel serosa. After resected the seeding part, the perforations were repaired by direct suture. The third patient underwent Hartmann's procedure revision, and the rectal re-anastomosis site leaked even with a proximal ileostomy diversion.

As noted above, the second most common complication is fistula, including enterocutaneous fistula and entero-bladder fistula. Two of the patients developed fistulas within 60 days, and one underwent reoperation for enterocutaneous fistula repair.

We usually transferred the patients after HIPEC therapy to the intensive care unit after the procedure because the cytoreductive surgery often caused multiple organ injuries during the procedure. In addition, HIPEC therapy caused hyperthermia injury and leukopenia, and some patients developed respiratory distress or neutropenic fever. However, these patients usually were transferred back to the ordinary care ward within 1 week.

Analysis of the mortality cases showed that three patients did not receive complete cytoreductive surgery, and their deaths could have been caused by disease progression. However, one of the patients also had postoperative bowel leakage, which led to the patient's death within 9 days after HIPEC therapy. The other two patients had colon cancer recurrences with peritoneal metastasis. One of these patients exhibited persistent pylorus leakage even after repair, and the other patient noticed recto-bladder fistula during long-term follow-up. Both patients expired under respiratory distress condition.

The delivery of intraperitoneal chemotherapy can be performed by using an "open" or "closed" approach. The open system usually used the Colisetum technique, which was proposed by Surgarbaker.[23] However, we used the closed system as an intraperitoneal chemotherapy method. Compared with the open system, the closed system can achieve the required temperature more rapidly and reduce heat dissipation. Moreover, it can decrease the volatilization of chemotherapy drugs into the air, which may cause harm to the operators. However, the surgical wound needs to be closed and drain tubes placed before HIPEC therapy, and an absorbable adhesion barrier could not be placed because it would dissolve in the solution. If the patient needed to undergo re-operation, adhesion to the raw abdominal wall would be a disaster. Additionally, the suction drain tube side-hole would easily be incarcerated by the omentum or intra-abdominal organ. Occasionally, removal of the drain is difficult after the procedure.

There were some limitations in this study. First, the follow-up time was insufficient for determining survival benefits. Second, the number of patients was small. Because the procedure in each case took a long time, including at least 1 h to perform HIPEC, it was difficult to complete many procedures in a short period. Additionally, the patient's cost is higher when a closed system of intraperitoneal chemotherapy is used because the expense is not included in health insurance payments. This extra cost may prevent a patient from receiving such treatments. Third, the criteria for HIPEC therapy and the intraperitoneal chemotherapy regimen are not well established. More time is needed for follow-up, and more cases must be accumulated to accurately assess the benefits of HIPEC therapy.

Conclusion

The complication rate of HIPEC therapy was found to be acceptable to the patients with peritoneal metastasis.

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原　著

大腸直腸癌合併腹膜內轉移之病人接受腹腔內高溫化學治療的可行性與短期預後

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目的　本研究之目的對於大腸癌腹膜內轉移的病人，在進行腹膜內高溫化學治療後之合併症與短期內追蹤之情形。

方法　收集於西元 2015 年 7 月至 2016 年 4 月間，大腸直腸癌合併腹膜內轉移之患者於台大醫院進行腹膜內高溫化學治療至少一小時。總共包括 22 名病患，針對其術後狀況進行分析。

結果　在這 22 名病患中，共有 18 名病人接受了腫瘤廓清手術。在追蹤的期間內，5 名 (22.7%) 病人在術後死亡；術後的併發症包括腸皮廔管 (13.6%)、吻合處滲漏 (9.1%)、肋膜積液 (9.1%)、輸尿管狹窄 (4.5%)、以及腸－膀胱廔管 (4.5%)。

結論　實施腹膜內高溫化學治療術後的病人其併發症仍可在接受範圍內。

關鍵詞　腹腔內化學治療、腹膜轉移。