Overview on Gastric Cancer

Chapter 6

Management of Peritoneal Metastases Originated from Gastric Cancer

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Abstract

Peritoneal Surface Malignancies (PSM) indicate the intraabdominal dissemination of neoplasms to the peritoneal surfaces and are previously was named as peritoneal carcinomatosis. Cytoreductive surgery and intraperitoneal chemotherapy have been introduced to the management of peritoneal metastases (PM) over 30 years. This novel approach became a standard of care for Pseudomyxoma Peritonei (PMP) originated from appendiceal or ovarian cancer, peritoneal metastasis of colorectal cancer and peritoneal mesothelioma. Here, management of PM developed from Gastric Cancer (GC) will be presented using cytoreductive surgery and intraperitoneal chemotherapy applications.

Keywords: Gastric cancer; Peritoneal metastasis; Cytoreductive surgery; HIPEC; Peritonectomy

Definition

Peritoneal Metastasis (PM) of Gastric Cancer (GC) describes the intraabdominal dissemination of gastric neoplasms to the peritoneal surfaces. PM of GC has been considered as a terminal stage of the disease and treated with palliative intent. More recently, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) have been introduced to treatment of peritoneal metastasis of epithelial carcinomas and peritoneal mesothelioma. Management of PM from GC will be presented using cytoreductive surgery and intraperitoneal chemotherapy applications.

In this novel algorithm, staging laparoscopy is performed. Peritoneal Cancer Index (PCI) is determined preoperatively. When the PCI level is more than 6, laparoscopic Hyperthermic Intraoperative Intraperitoneal Chemotherapy (HIPEC) is performed and intraperitoneal port is placed and are treated with bidirectional neoadjuvant intraperitoneal and systemic chemotherapy (NIPS) for 4-6 cycles to downstage the disease. When the PCI level is less than 6, complete cytoreductive surgery and HIPEC are performed.

The operation is two step process:

1. Surgical Resection of involved organs and peritoneum, then

2. Heated chemotherapy solution is circulated in the abdominal cavity to treat any cancer cells that may remain after surgery.

Thus, aim of this technique is that to treat macroscopic diseases with maximum surgical resections in order to achieve complete cytoreduction and to treat microscopic disease with heated circulated chemotherapy.

Prospective randomized studies are needed to be performed to select the patients who can expect to have a benefit from these complex procedures.

1. Introduction

Gastric Cancer (GC) is the fifth most common cancer and the third most common cause of death from cancer in the world [1]. The curative treatment of choice for GC remains surgery with adjuvant systemic chemotherapy. GC has the highest rate of peritoneal metastasis (PM) among intraabdominal cancers. Approximately 10-20% of patients with Gastric Cancer (GC) are detected to have PM at the time of initial diagnosis [2]. PM is the only site of metastasis in 68.6% of GC cases [3]. PM is detected as a recurrence in 36-45.9% of patients with GC after curative treatment [4,5]. Factors are detected to be associated with PM include tumor stage (T3/T4) [6,7], presence of free cancer cells [8] and lymph node involvement [9], and signet ring cell adenocarcinoma [10].

2. Molecular Background of Peritoneal Metastasis of Gastric Cancer

Spontaneously exfoliated or iatrogenically disseminated endoperitoneal free cancer cells adhere to the surface of intraabdominal organs and walls which are trapped by fibrin and stimulated by growth factors due to the wound healing. This process is called as "Tumor cell entrapment hypothesis" proposed by Sugarbaker [11]. These intraperitoneal seeded nodules become hypoxic and may also become resist to systemic chemotherapy.

Endoperitoneal free cancer cells can also diffuse to the "Milky Spots" which are little cribriform "stomata" present on the peritoneal surface consists of macrophages and B1 cells. Milky spots are localized in the omentum and sub diaphragmatic areas [12]. Endoperitoneal free cancer cells are trapped to the spots and became hypoxic nodule [13].

Molecular mechanism of PM of GC is not clear yet. Chemokines (CXC) and growth factors may play a role in mechanism of PM from GC [14]. CXCR4/CXCL12 axis is involved the PM of GC. Elevated expression of CXCR4 in tumor tissue significantly correlates with occurrence of PM. CXCR4-expressing GC cells are attracted to the peritoneal surfaces where its ligand CXCL12 is overexpressed in these surfaces [14].

3. Treatment of Peritoneal Metastasis of Gastric Cancer

Gastric cancer has the highest incidence of peritoneal metastases in gastrointestinal cancers. The main reason for treatment failure is peritoneal recurrence following curative surgery. PM of GC has been treated with palliative treatment as a consequence of thought that is incurable disease. The prognosis of PM of GC is very poor with a median survival after diagnosis is limited to several months. Once PM occurs, response rate of the tumor is decreased to the systemic chemotherapy [15]. The decreased response rate is attributed to the presence of plasma-peritoneal barrier which isolates the peritoneal cavity from the intravenous chemotherapy [16].

4. Cytoreductive Surgery and hyperthermic intraoperative intraperitoneal chemotherapy

PM has been considered as a loco-regional metastasis of the intraabdominal organs that can be treated with cytoreductive surgery (CRS) and hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC). Intraperitoneal chemotherapy has the advantage of direct exposure of intraabdominal tumor cells to the chemotherapeutic agents while they are small or non-vascularized or free in the peritoneal cavity. Therefore, direct contact of cancer cells to the chemotherapy agents also avoids the high risk of toxicity caused by systemic chemotherapy.

Direct cytotoxic effects of hyperthermia have been demonstrated *in vitro* [17] and also

hyperthermia increases the effectiveness of certain molecules [18].

Complete CRS and HIPEC seems to be the only treatment option to achieve long-term survival for peritoneal metastasis.

Table 1: Effectiveness of CRS and HIPEC in patients with PM of GC

Authors	Number of Patients	Chemotherapy Agents in HIPEC	Morbidity/ Mortality	Survival
Fujimoto et al. (20)	15	MMC	-	7.2±4.6 mo
Yonemura et al. (21)	41	MMC+CDDP	29.3% - 0	28.5% for 3-year
Fujimoto et al. (22)	48	MMC	-	31% for 5-year 25.4 % for 8-year
Hirose et al. (23)	17	Etoposide	35.2% - 5.8%	44.4% *vs* 15.8% HIPEC *vs* control group in 1-year
Glehen et al. (24)	49	MMC	27% - 4%	Overall 16% 29.4% in CC-0/1 resection in 5-year
Hall et al. (25)	34	MMC	35% - 0%	45% in CC0/1 resection in 2-year 8% in CC2/3 resections 6.7% for 5 year period
Yonemura et al. (26)	107	MMC+CDDP	21.5%-2.8%	6.7 % for 5-year
Scaringi et al. (27)	26	CDDP	27%-3.8%	15 mo for CC-0 & 3.9 moCC-2 (MS)
Glehen et al. (28)	139	MMC±CDDP Or LOHP±Irinotecan	27.8%-6.5%	13% for 5-year survival 23% for CC-0 resection
Yang et al (29)	RCT (34 pts)	MMC+CDDP	14.7%-0	5.9% for 3 y 23% for CC0/1
Magge et al (30)	23	MMC+CDDP	52.2%-4.3%	50% for 1-year 18% for 3 year
Rudloff et al (31) GYMSSA trial	RCT	LOHP	-	11.3 months for Median OS vs 4.3 months in CT arm

Peritonectomy procedures are performed during surgery to remove the affected peritoneum and to achieve complete cytoreduction. Aim of the peritonectomy and complete cytoreduction is to obtain optimal therapeutic effects of HIPEC. The residual disease is

calculated using completeness cytoreduction (CC) score [19].

5. CC Score Definition

Treatment of PM of GC with cytoreductive surgery and HIPEC is still under the investigation. Several studies suggest that the possible long-term survival in patients with complete cytoreductive surgery. Studies performed to evaluation the effectiveness of CRS and HIPEC in patients with PM of GC are given in time dependent manner in Table-1.

Completeness of cytoreduction is the independent prognostic factor in patients with PM of GC [26,28]. In a systematic review, it has been reported that median overall survival is increased to15 months in case of complete cytoreduction achieved and 5-year survival is 13% in patients with PM of GC [32]. Phase III randomized study conducted to compare the effects of CRS and HIPEC in patients with PM of GC [29]. They showed that median survival was increased to 11 months in CRS&HIPEC group compared to 6.5 months in CRS alone group. In recent prospective randomized clinical trial GYMSSA study, median overall survival was 11.3 months compared to 4.3 months in CRS alone group even though small number of patients were enrolled the study. There is no survivor in the systemic chemotherapy arm after 11 months. Four out of 7 patients were alive more than 12 months, 2 patients close to 2 years, 1 patient more than 4 years with 2 of these patients are still alive. All survivors had an initial Peritoneal Cancer Index less than 15 and they all had a complete cytoreduction.

These results are promising that outcomes of patients with PM of GC might be increased with CRS&HIPEC and PM of GC can be even cured. Limited extension of the disease and complete cytoreduction seem to be the indication of CRS and HIPEC in these patients with PM of GC [28] .

Today, HIPEC indications are changing through to adjuvant or prophylactic setting in patients with PM of colorectal cancer. In near future, HIPEC indications will be changed for GC cases. This theory is supported by several studies. Approximately 60% of patients with GC involved serosa will develop PM [32]. It has been reported that a potential benefit from intraperitoneal chemotherapy with or without hyperthermia as a complementary treatment to curative surgery [33,34].

Effect of intraperitoneal chemotherapy on peritoneal metastasis developed as a recurrence of resectable gastric cancer has been investigated in several studies (Table-2). Fujimoto et al. [35] reported that HIPEC significantly reduced peritoneal recurrence. Yonemura et al. [36] showed that overall survival is increased up to 61% when HIPEC was added in adjuvant setting to surgery. Kim and Bae [37] published 5-year survival is significantly increased in GC patients with invasion of the serosa when they were treated with HIPEC in addition to surgery.

Table 2: Survival effects of intraperitoneal chemotherapy in adjuvant setting to primary surgery for prevention of development PM in patients with GC.

Authors	**Number of Patients** **CRS&HIPEC vs CRS**	**Survival** **2-4- and 8-years** **CRS&HIPEC vs CRS**	**Survival benefit** **P value**
Fujimoto et al (35)	141 CRS&HIPEC vs CRS 71 vs 70	2-4- and 8 year survival 88%-76%-62% vs 77%-58%-49%	P=0.03
Yonemura (36)	CRS&HIPEC vs CRS vs Intraperitoneal chemotherapy	5 year survival 61%-43%-42%	p<0.05
Kim and Bae (37)	103 51vs 52 CRS vs CRS+HIPEC	5-year survival 32.7%- 27.1%	p<0.05

Effects and safety of adjuvant intraperitoneal chemotherapy with locally advanced resectable gastric cancer was investigated in meta-analysis [38]. Patients with gastric cancer were included this meta-analysis whom were randomly assigned to receive surgery combined with intraperitoneal chemotherapy versus surgery without intraperitoneal chemotherapy. Ten reports were analyzed and there was a trend towards survival improvement with normothermic intraperitoneal chemotherapy ($p = 0.06$), but this effect was not time dependent. There was no significant difference between application of intraperitoneal chemotherapy in early postoperative time and delayed postoperative time. Finally, this meta-analysis indicates that intraperitoneal chemotherapy after resection of advanced Gastric Cancer is associated with improved overall survival with time independent manner. However, increased risk of intra-abdominal abscess and neutropenia are also demonstrated. Sun et al. [39] published the result of meta-analysis on the effects of HIPEC in patients with GC involved serosal surfaces. They reported the significant improvement in survival and decrement in peritoneal recurrence rate in HIPEC group in advanced GC cases. Coccolini et al. [40] published the meta-analysis result that also demonstrated the potential benefit of using HIPEC as an adjuvant treatment to advanced gastric cancer.

6. Intraperitoneal Free Cancer Cells and Its Importance

It is established that presence of peritoneal free cancer cells is associated with depth in invasion of the gastric wall that is also associated with poor prognosis [41]. Presence of free

peritoneal cells are associated with an average survival of 4 months compared to 21 months in patients without positive cytology [42]. Peritoneal cytology is important in staging and management of advanced GC [43].

Even though the cytology is negative in peritoneal washing, peritoneal seeding can be detected with using reverse transcriptase-polymerase chain reaction analysis. Indeed, Fujiwara showed the importance of molecular diagnosis in GC patients with poor prognosis [44]. Approximately two of three patients will have positive with PCR diagnosis while they all are negative in cytological examination and PCR positivity is correlated with short term of overall survival and peritoneal recurrence [45,46].

7. Intraperitoneal chemotherapy plus systemic chemotherapy as neoadjuvant setting in management of Peritoneal metastasis of gastric cancer

Yonemura et al. [26] reported a retrospective study on 107 patients with PM of GC. They have used intraperitoneal cisplatin chemotherapy in neoadjuvant setting and performed cytoreductive surgery and HIPEC to responders. Aim of this study was to evaluate the effects of neoadjuvant intraperitoneal chemotherapy applications prior to surgery and HIPEC on overall survival in patients with PM of GC. They have found that median survival was 15.5 months in the group with complete cytoreduction while 7.9 months in the group with incomplete cytoreduction following neoadjuvant intraperitoneal chemotherapy. And, 5-year survival was 27% in the group achieved complete cytoreduction while 6.7% in patients with incomplete cytoreduction. Yonemura and his group concluded that intraperitoneal chemotherapy combined with systemic chemotherapy in neoadjuvant setting prior to CRS and HIPEC is increased overall survival in the patients with PM of GC when completed cytoreductive surgery was achieved.

Canbay et al. [47] reported the results of evaluation bidirectional induction chemotherapy (bidirectional intraperitoneal and systemic induction chemotherapy (BIPSC) in patients with PM of GC who underwent cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) in neoadjuvant setting. One hundred ninety four patients were treated with BIPSC of these patients, 152 (78.3 %) underwent CRS and the median survival rate was 15.8 months. Multivariate analysis showed that pathologic response to these combined treatment approach ($p = 0.001$), low tumor burden [peritoneal cancer index (PCI) ≤ 6] ($p = 0.001$), and completeness of CRS (CC-0, CC-1) ($p = 0.001$) as independent predictors for a better prognosis.

Finally, they conclude that bidirectional induction chemotherapy in neoadjuvant setting may be performed safely, with acceptable morbidity and mortality, in a specialized unit. Response to this treatment prior to CRS and HIPEC and complete CRS and limited peritoneal disease seem to be essential for better outcomes in patients with PM of GC.

Since then the group hypothesized to improve induction therapy to get better outcomes

in patients with PM of GC. The Peritoneal Surface Oncology Group International (PSOGI) suggested a comprehensive management approach consisting of CRS and HIPEC for the treatment of PM of GC as a curative intent [48]. In this strategy, diagnostic laparoscopy was performed and peritoneal cancer index (PCI) was determined. If PCI level was more than 6, a peritoneal port was placed. Neoadjuvant bidirectional intraperitoneal/systemic chemotherapy (NIPS) was initiated two weeks after laparoscopy. Laparoscopy was performed and PCI level was less than 6, cytoreductive surgery was performed to remove all macroscopically observable disease and HIPEC were added for microscopic residual disease. Then, these patients were treated with adjuvant chemotherapy. Even though the PSOGI published the comprehensive treatment modality with proven efficacy, unfortunately, outcome of these studies are results not completely accepted by all surgeons. Outcomes of randomized clinical trials with large sample size will clarify the exact role of this approach in management of PM of GC.

8. Conclusion

PM of GC has a poor prognosis that has been considered to lethal disease and treated palliative systemic chemotherapy. However, CRS and HIPEC to add the systemic treatment approach can increase overall survival in selected patients. Learning curve for a center to perform CRS and HIPEC is 140-220 cases and for indivudual surgeons about 33 to 70 cases [48].

9. Recommendations

1. PM of GC should be discussed in multidisciplinary team
2. PM of GC should be considered to manage with CRS and HIPEC in physical fit patients
3. Diagnostic laparoscopy should be performed in each cases of GC
4. If cytology is positive and/or PCI is less than 6 is considered as resectable PM of GC cases, CRS and HIPEC should consider in the management of these patients
5. If PCI is more than 6, laparoscopic HIPEC is performed and ip port is placed and the patients are treated with bidirectional chemotherapy until PCI score is decreased. Then, CC-0 resection and HIPEC are performed in patients with pathological response and PCI level less than 6.
6. Prospective randomized studies are needed to be performed to select the patients who can expect to have an optimal benefit from these complex procedures.

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