Conversion Therapy for Gastric Cancer with Peritoneal Metastasis

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ABSTRACT

Peritoneal metastasis in gastric cancer has a poor prognosis and is increasing in prevalence. Neoadjuvant chemotherapy is used for advanced tumors; however, surgery is generally not considered for metastatic and unresectable diseases. Recently, conversion surgery, a treatment which aims for an R0 resection following chemotherapy, has become a novel therapeutic option with better survival rates. In addition to surgery, hyperthermic intraperitoneal chemotherapy (HIPEC) leads to significant tumor reduction, but it is limited by its morbidity. Pressurized intraperitoneal aerosol chemotherapy (PIPAC) delivers high concentrations of chemotherapy, but does not remove the tumor, making it useful mostly in palliative settings. Intraperitoneal (IP) therapy, known for its minimally invasive nature and repeatability, shows promise but requires further research. Ultimately, an integrated approach involving systemic chemotherapy, radical gastrectomy, HIPEC, PIPAC and IP chemotherapy can be used to optimize treatment outcomes of gastric cancer patients with peritoneal metastasis.

Keywords: Gastric cancer; conversion surgery; HIPEC; peritoneal metastasis (Siriraj Med J 2024; 76: 534-540)

INTRODUCTION

Peritoneal metastasis from gastric cancer is associated with an extremely poor prognosis. In recent years, there has been a notable increase in the prevalence of peritoneal metastasis, with *Koemans* reporting that the incidence rate rose from 18% in 2008 to 27% in 2017. Furthermore, the median survival duration has remained unchanged at 9.4 months over this period.[1] According to a study by *Ikoma*, among the 488 patients with gastric cancer who underwent curative gastrectomy, peritoneal metastasis was the most prevalent site of recurrence (49%).[2] Furthermore, peritoneal metastasis in gastric cancer patients was associated with lower survival rates compared to liver metastasis.[3] In Thailand, despite the fact that the majority of gastric cancers are diagnosed at advanced stages, radical gastrectomy can still yield favorable survival results, with acceptable rates of postoperative complications, particularly when an enhanced recovery after surgery protocol is followed.[4] However, once peritoneal metastasis develops, surgery cannot be performed, and a patient's prognosis significantly worsens.

Patients with gastric cancer typically undergo gastroscopy and a computerized tomography scan to determine disease stage. Diagnostic laparoscopy is particularly valuable in identifying peritoneal metastases in cases of advanced gastric cancer. According to a

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meta-analysis, diagnostic laparoscopy has a sensitivity of 84.6% and specificity of 100%.[5] It has been able to alter therapeutic approaches in 8.5%–59.6% of patients and prevented unnecessary surgery in 8.5%-43.8% of cases.[6] To get the best results, diagnostic laparoscopy must be performed thoroughly and systematically, including examining the anterior abdominal wall, pelvic cavity, mesentery, small intestine, stomach, and omental bursa.[7] Diagnostic laparoscopy is particularly recommended for patients with a Borrmann type 3 or 4 tumor or when there is the presence of bulky lymph nodes.[8] Diagnostic laparoscopy also plays a crucial role in determining the appropriate chemotherapy regimen. The presence of a peritoneal nodule warrants the use of the FLOT regimen, which consists of fluorouracil, leucovorin, oxaliplatin, and docetaxel.[9] In the absence of peritoneal metastasis, a combination of fluorouracil and oxaliplatin is recommended.

Conversion therapy

The REGATTA study, a large-scale clinical trial involving patients with stage IV gastric cancer, evaluated the outcomes of combining gastrectomy and chemotherapy versus chemotherapy alone. The study included a diverse sample of patients, each with a single, incurable factor (liver, peritoneal, or paraaortic lymph node involvement). The findings revealed that combination treatment did not significantly improve survival rates compared to chemotherapy alone. As a result, palliative chemotherapy is now considered the standard of care approach for patients with stage IV gastric cancer.[10,11] However, despite this, the median survival time achieved with palliative care remains unsatisfactory.

In 1977, *Nakajima* introduced the concept of conversion surgery at Japan's Cancer Institute Hospital for patients with stage IV gastric cancer who demonstrated a complete clinical response, a partial response, or stable disease after receiving palliative care. These patients underwent gastrectomy, lymphadenectomy, and metastasectomy, resulting in a longer median survival time and an increased likelihood of achieving complete tumor removal (R0 resection).[12] Thus, conversion surgery is defined as a surgical technique designed to achieve an R0 resection following chemotherapy. It is used in cases of stage IV gastric cancer that were initially deemed unresectable or only marginally resectable due to technical or oncological challenges. This strategy presents a potentially viable option for patients with tumors that were previously considered unresectable or marginally resectable. By aiming to achieve R0 resection following chemotherapy, conversion surgery aims to improve patient outcomes and potentially increase survival rates. However, it is important to note that conversion surgery may not be suitable for all patients, as its success rate varies depending on factors such as the extent of peritoneal metastasis and a patient's response to chemotherapy.

Conversion therapy can be performed in one or more of the following methods:

- Systemic chemotherapy
- Hyperthermic intraperitoneal chemotherapy (HIPEC)
- Pressurized intraperitoneal aerosol chemotherapy (PIPAC)
- Intraperitoneal (IP) chemotherapy

Yoshida et al. identified four types of conversion therapy based on incurable factors, such as T4b lesions, non-regional lymph node metastasis, hepatic metastasis, and peritoneal metastasis.[13] He initially categorized stage IV gastric cancer patients into two groups based on the presence or absence of macroscopic peritoneal spread. Categories 1 and 2 comprised patients without macroscopic peritoneal dissemination, while categories 3 and 4 included the presence of macroscopic peritoneal dispersion. Patients with liver metastasis, distant organ metastasis or paraaortic lymph node metastasis, but without visible macroscopic peritoneal metastasis (categories 2), were categorized as marginally resectable gastric cancer. In contrast, those with visible macroscopic peritoneal metastasis (categories 3 and 4) were classified as unresectable gastric cancer. After chemotherapy, conversion surgery has shown about a 70% success rate in tumor removal in categories 1–3, but only 50% in category 4. Furthermore, the overall survival rate in all categories sees an improvement if conversion surgery and R0 resection are successful, with five-year survival rate for each group ranging from 30% to 40%. Overall, category 2 has the highest survival rate.[14]

The 2018 Chicago consensus provides guidelines on the use of conversion surgery for gastric cancer patients with peritoneal metastasis.[15] It outlines the role of conversion surgery in cases where chemotherapy is the primary treatment choice. According to the consensus, conversion surgery, including cytoreduction surgery, gastrectomy, and intraperitoneal chemotherapy, is viable if a patient's condition is stable, and they have a low peritoneal carcinomatous index (PCI). The PCI score divides the abdomen into nine regions and the small bowel into four, with scores ranging from 0 to 3 in each area. This helps surgeons assess the extent of peritoneal metastases during surgery.[16] However, patients exhibiting a high PCI score following laparoscopic intraperitoneal chemotherapy or neoadjuvant intraperitoneal and systemic

treatment, gastrectomy alone is recommended. These recommendations help medical professionals make informed decisions about the use of conversion surgery based on an individual patient's characteristics and circumstances.

Systemic chemotherapy

Systemic chemotherapy serves as an initial treatment for metastatic gastric cancer, as it can help reduce tumor size and slow down disease progression. A critical component of this treatment is identifying tumor biomarkers, which inform treatment decisions and pinpoint the most effective medication to use. Key biomarkers include Human Epidermal Growth Factor Receptor 2 (HER2), overexpression and Programmed Death-Ligand 1 (PD-L1), with a Combined Positive Score greater than five (CPS >5), and microsatellite instability (MSI).[17] The CPS method assesses biomarker expression, such as PD-L1 in cancer tissue, by combining the expression levels from both tumor cells and immune cells, which aids treatment decisions, particularly for immunotherapy.[18] These biomarkers play a crucial role in guiding targeted therapies for metastatic gastric cancer. For example, HER2-positive tumors may respond well to HER2-targeted therapies such as trastuzumab, while tumors with high PD-L1 combined positive score may benefit from immunotherapies such as pembrolizumab. Additionally, microsatellite instability (MSI) can indicate the potential efficacy of immune checkpoint inhibitors such as pembrolizumab. The anticipated inclusion of claudin 18.2 as a biomarker will further refine treatment decisions and enable personalized approaches for patients with metastatic gastric cancer. Platinum and fluoropyrimidine-based chemotherapy remain the primary systemic chemotherapy options for metastatic gastric cancer. HER2-positive patients may also receive trastuzumab. After four sessions of systemic chemotherapy, patient eligibility for conversion therapy is reassessed using diagnostic laparoscopy and computed tomography. If peritoneal metastasis persists, patients should be considered for second-line treatments: MSI-high patients are given pembrolizumab, whereas those without MSI-high status are given paclitaxel and ramucirumab. Following an additional four courses, patients are reevaluated. If carcinomatosis continues, a third line of treatment will be administered. However, if reevaluation reveals support for conversion surgery, patients may proceed with cytoreductive surgery complemented by HIPEC.

Kano reported on conversion surgery in 79 stage IV gastric cancer patients, achieving an R0 resection rate of 79.7% with a 3-year survival rate of 44.5%,[19] whereas *Beom's* study found an R0 resection rate of 56.4% among patients, with a median survival time of 26 months.[20] Recent data indicates that the efficacy of conversion treatment can achieve an R0 gastrectomy that ranges between 34.4%-75%, with a median survival time of 19.2-62 months in those who achieve R0 resection.

Hyperthermic intraperitoneal chemotherapy (HIPEC)

This technique involves administering heated chemotherapy directly into the abdominal cavity after removing visible tumors during surgery (Fig 1). The elevated temperature enhances the chemotherapy's effectiveness through increased drug activity and deeper tissue penetration. However, HIPEC's effectiveness is limited to nodules not exceeding 2.5 mm in size. HIPEC is contraindicated in patients with distant metastases, high PCI scores, or those unfit for surgery. According to a German study,[20] cytoreductive surgery combined with HIPEC can increase survival by 17%. Moreover, neither HIPEC nor cytoreductive surgery should be used in isolation; the two should be combined. *Yonemura* suggested this combined approach for patients with PCI scores less than 6.[21] The GYMMSA trial,[22] which compared chemotherapy to HIPEC surgery, observed median survival increase from 4.3 months to 11.3 months in the HIPEC group. Moreover, HIPEC surgery plays an important role in complete cytoreduction as found by Glehan in a study that showed an extension of median survival to 15 months, with an overall median survival of 9.2 months, 61% survival at one year, and 23% at 5 years.[23] A meta-analysis of 23 studies and 1,892 patients, demonstrated that HIPEC surgery led to higher survival rates at 1 year, 2 years, and 3 years compared to systemic chemotherapy, and increased median survival time by 4.67 months in the HIPEC group.[24]

At Siriraj Hospital's Department of Surgery, we treated 20 patients with gastric cancer and peritoneal metastasis from April 2013 to March 2020. HIPEC was administered using an open technique with cisplatin and mitomycin-C as chemotherapeutic agents at 42°C for 60 minutes. After one year, the overall survival rate was 73.90%, and after three years, it was 9.60%. This demonstrates that HIPEC can significantly enhance survival rates with manageable complications. However, due to prolonged duration and potential risks of the procedure, careful patient selection is imperative.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC)

Chemotherapeutic drugs delivered through PIPAC utilize pressured aerosols to enhance penetration into

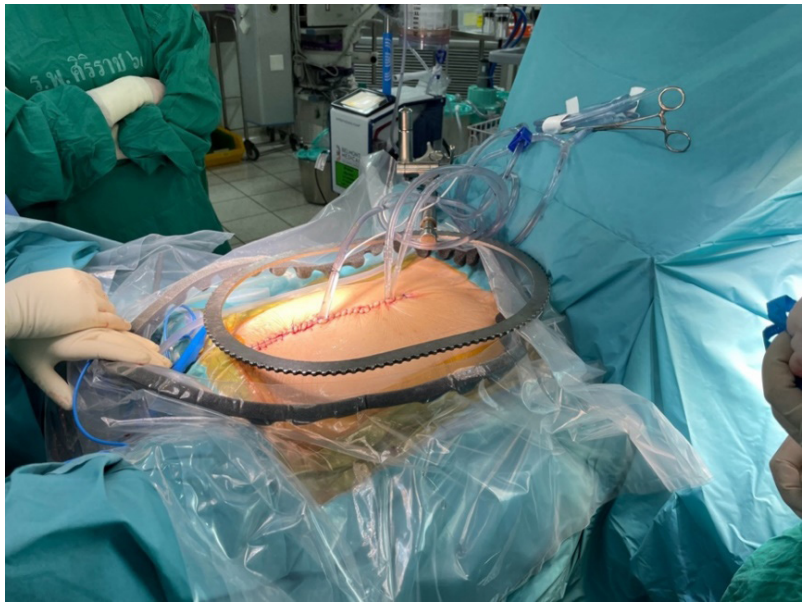

Fig 1. A demonstration of the inflow and outflow catheters connecting to the HIPEC machine.

cancer cells and optimize distribution. After laparoscopy, a specialized nebulizer device is connected to a high-pressure injector and then inserted into the peritoneal cavity via a trocar (Fig 2). Aerosols of cisplatin and doxorubicin aerosols are applied under pressure and maintained for 30 minutes. This method has been deemed safe during the procedure,[25] and its effectiveness in treating peritoneal metastases has been demonstrated with observed regression of peritoneal nodules.[26] In a systematic review by Case involving 751 patients with gastric cancer and peritoneal metastases treated with PIPAC, the median survival time ranged from 8-19.1 months, with a 1-year survival rate between 49.8-77.9%.[27] Complete response rates varied from 0% to 35%, and grade 3 and 4 toxicities ranged between 0.7% to 25% and 0%-4.1%, respectively. The advantage of PIPAC is that it enables repeated dosing and improves quality of life with minimal complications since no invasive surgery is required.

Intraperitoneal (IP) therapy

Intraperitoneal (IP) therapy involves administering drugs directly into the peritoneal cavity using a peritoneal implantable port system (Fig 3). This delivery method enables higher drug concentrations in the peritoneal fluid, leading to improved local disease control. The ability to administer repeated doses directly to the peritoneal cavity may improve the quality of life of patients with stomach cancer and peritoneal metastases. IP therapy can be used simultaneously with or after systemic chemotherapy if HIPEC surgery is not possible due to a PCI score of more than six. A high PCI score indicates significant cancer spread within the peritoneal cavity and complicates HIPEC surgery. However, IP therapy remains a viable treatment option for these patients.

Paclitaxel is often included in the IP therapy regimen due to its prolonged intraperitoneal retention, combined with intravenous paclitaxel and oral S-1. Typically, three

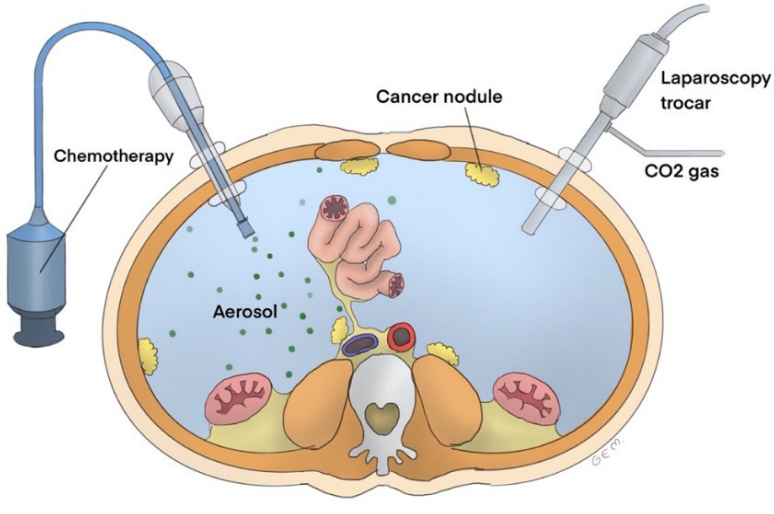

Fig 2. Schematic representation of the Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC) procedure. This schematic illustrates the process of delivering chemotherapy directly into the peritoneal cavity using pressurized aerosolization.

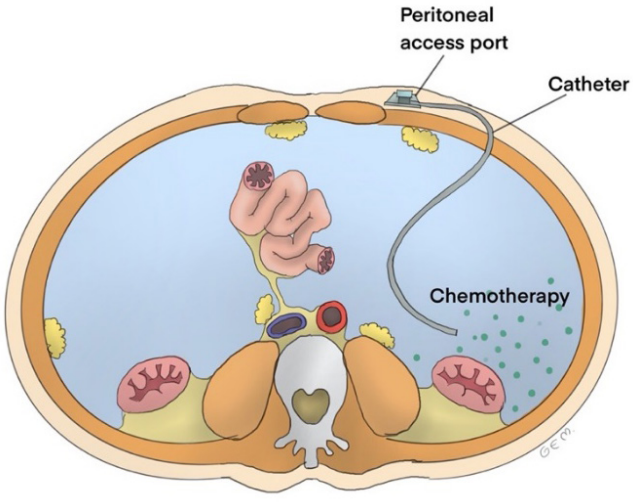

Fig 3. Illustration of catheter placement for intraperitoneal (IP) chemotherapy administration.

sessions of IP therapy precede diagnostic laparoscopy to assess peritoneal nodules. According to Ishigami's study,[28] 64% of patients who received IP therapy were able to undergo gastrectomy with an R0 resection rate of 69%, and a median survival time of 30.5 months. Additional research highlights IP therapy's effectiveness, showing a cytology negative conversion rate of 71%-97%, a median survival time of 15.1-24.6 months, and 1-year overall survival rate of 70.4%-78%.

Ishigami's Phoenix gastric cancer trial in 2018 compared the effectiveness of intraperitoneal and systemic chemotherapy for P1 gastric cancer with peritoneal metastasis.[29] The study compared intraperitoneal and intravenous paclitaxel and S-1 with intravenous paclitaxel and S-1, or S-1 and cisplatin. Despite prolonging the median survival time by 2.5 months and a reported hazard ratio of 0.72, the trial failed to show statistical significance. Future research may be able to demonstrate the statistical significance of this treatment strategy and provide better treatment options for patients with advanced gastric cancer.

The management protocol in gastric cancer with peritoneal metastasis

Each therapy has its own characteristics. HIPEC can achieve maximum elimination of cancer cells in the abdomen by delivering a high concentration of intraperitoneal drug which facilitates excellent drug penetration into the cancer cells. However, it is a one-time procedure and is linked with significant complications. It is recommended for patients with minimal peritoneal metastasis (PCI<6). PIPAC offers a high concentration of intraperitoneal drug and the advantage of being repeatable. Nonetheless, PIPAC does not eliminate gross tumor mass, and therefore, its main role is in a palliative care setting. Moreover, the procedure involves high-pressure injection of chemotherapeutic drugs, which requires a well-trained and certified PIPAC team. IP therapy allows for prolonged exposure to chemotherapeutic drugs and is repeatable. It can be used for tumor downstaging in conversion therapy or for palliative care, however, these roles have to be determined in future studies.

These methods are combined to optimize tumor reduction in gastric cancer with peritoneal metastases. The treatment flow protocol for gastric cancer with peritoneal metastasis is depicted in Fig 4. The process begins with diagnostic laparoscopy to confirm the presence of peritoneal metastases, followed by the initiation of systemic chemotherapy. A subsequent diagnostic laparoscopy assesses PCI and if it is less than 6, the patient may undergo radical gastrectomy combined with peritonectomy and HIPEC. If PCI exceeds 6, systemic treatment is maintained with a combination of PIPAC and IP chemotherapy. IP chemotherapy can also be used alongside systemic chemotherapy to enhance disease control.

CONCLUSION

Overall, the treatment for gastric cancer with peritoneal metastasis is multifaceted and depends on a patient's condition and response to different therapies. Although surgery can offer benefits to some patients, it is not the only solution. HIPEC provides substantial tumor reduction but it has limitations due to its non-repeatable nature and potential complications. PIPAC delivers a high concentration of medication directly to the peritoneum, but it does not remove the tumor. IP therapy has a longer drug exposure and can be repeated, but further research is still required to establish its role in the treatment. Ultimately, conversion surgery, utilizing a combination of systemic chemotherapy, radical gastrectomy, HIPEC, PIPAC and IP chemotherapy can be used to optimize treatment outcomes of gastric cancer patients with peritoneal metastasis.

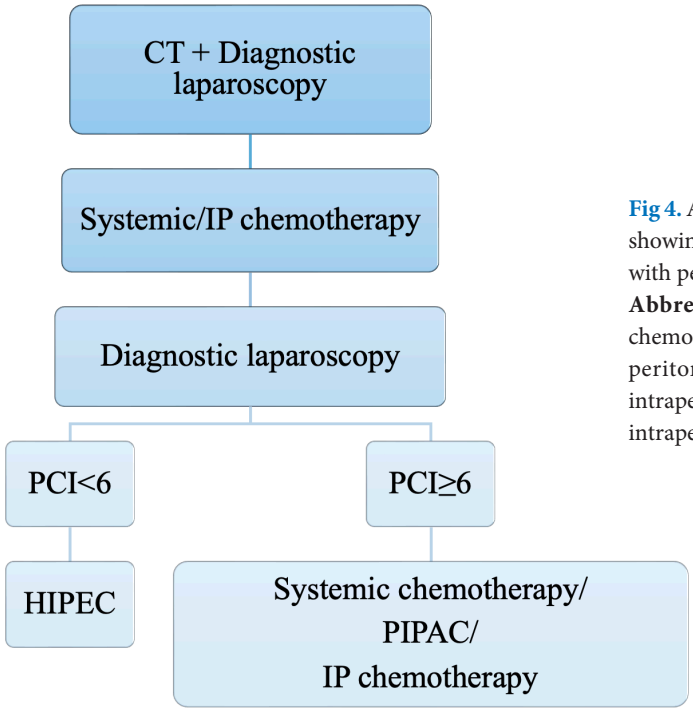

Fig 4. A flowchart based on the author's conclusions, showing the sequence of treatment for gastric cancer with peritoneal metastasis
Abbreviations: CT, computed tomography; IP chemotherapy, Intraperitoneal chemotherapy; PCI, peritoneal cancer index; HIPEC, Hyperthermic intraperitoneal chemotherapy; PIPAC, Pressurized intraperitoneal aerosol chemotherapy

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Author Contributions

Conceptualization: TI, AM; Data curation: TI, AM, CN; Investigation: TI, AM, TP; Methodology: TI, AM; Supervision: AM, TA, VC; Validation: TI, AM, AT; Visualization: JS, AT, CP, VT; Writing– original draft: TI, AM; Writing– review & editing: all authors.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that might have influenced the work presented in this paper.

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