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Peritoneal Metastasis from Gastric Cancer: State of Art

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Abstract

Peritoneal metastasis (PM) has traditionally been approached with therapeutic nihilism. Gastric Cancer is a lethal disease especially with the presence of PM. The standard treatment for Gastric cancer with PM is palliative systemic Chemotherapy with a survival of 6 months. The evolution of cytoreductive surgery (CRS) and hyperthermic intraoperative chemotherapy the last decade, however, has caused a paradigm shift in the treatment for PM. This article reviews the current literature date regarding the use of CRS/HIPEC for PM from gastric cancer.

Significance: Peritoneal Metastasis; Gastric Cancer; CRS; HIPEC

Introduction

Gastric Cancer remains a lethal disease and is the 3rd leading cause of death from cancer in the world [1, 2]. Peritoneal metastasis is the most common type of recurrence and cause of death in gastric cancer. Patients with locally advance disease (tumor penetrating deeper to mucosa) at time of diagnosis remain at high risk for peritoneal dissemination despite margin-negative resection [3]. Peritoneal disease are present in 20-30% at primary diagnosis and 40-60% will have a peritoneal relapse as the only site of metastasis the first 2 years after curative resection [4, 5]. On the other hand, the presence of positive peritoneal Lavage cytology is classified as M1 and has as similar prognosis to that of macroscopic metastatic nodules. The most common treatment with medical oncologists' guidelines recommend palliative systemic chemotherapy [6, 7] with poor survival outcomes. The role of CRS/HIPEC for gastric cancer has been evaluated both in an adjuvant setting for locally advanced disease with curative resection as well as in setting of peritoneal metastasis. There is an increasing evidence based mainly on retrospective information and in several prospective trials with encouraging survival results in selected cases. In this article we present the state-of-the-art opinions concerning the management of peritoneal metastasis in gastric disease.

The Important Role of PCI a Selection Factor

Given the aggressive native of gastric cancer, the importance of patient selection for CRS/HIPEC in this setting cannot be stressed enough. We currently offer Hipec only in patients with low disease burden. The two most important prognostic factors for patients with gastric cancer with PM are the volume of peritoneal disease, estimated by the PCI and the possibility to achieve a complete cytoreduction according to the completeness cytoreduction score [8, 9]. As both factors are related, PCI assessment is crucial to select patients for CRS and HIPEC. In 2010, Glehen O et. al. [10] published the analysis of 159 patients with PM from gastric cancer. No patient with PCI higher than 19 survived at 6 months and no patient with PCI>12 survived at 3 years. So, this French study recommended that patient with PCI>12 should not be treated with CRS and HIPEC because the survival benefit is extremely low. In 2016 Chia et. al. [11] published an analysis of 81 patients treated with complete CRS (CC0/1) and HIPEC. Patients with PCI<7 had a median OS of 26,4 months versus 10,9 month for PCI≥7. So in this study patients with a PCI<7 and a complete CRS, there is a real possibility of Cure. In 2019 a Spanish study of 88 patients with PM from gastric cancer have the similar results with PCI<7 had a median OS of 26,1 months versus 18,9 m with PCI>7

[6]. In the same study the 5-year survival rate was 46,8% with PCI<7 while those with PCI≥7 had a 5-year survival rate of 0%. More recently in 2020 Rau B et. al. [12] from Germany has been published with 235 patients. The median OS according to PCI was 18 months for PCI 0-6, 12 m for PCI 7-15 and 5 months with PCI 16-39.

Role of Systemic Chemotherapy

In western countries (Europe and USA) pre-and post-operative systemic chemotherapy is the standard of care. The MAGIC trial was published in 2007 has been the standard therapy of patients with advance gastric cancer. Unfortunately, the role of this trial in patients with PM offers a median OS benefit of 5,4 months in patients with low cancer volume [13]. The 2019 the publication of FLOT4 trial has changed this standard of care and currently the FLOT (Fluorouracil, leucovorin, oxaliplatin and docetaxel) with 4 preoperative and 4 postoperative cycles is preferred. The benefit of FLOT in localized tumors with peritoneal disease offers a median OS 9,8 [14].

Neo Adjuvant Intraperitoneal Chemotherapy

In early 2000 Japanese studies proposed the combination of neoadjuvant intraperitoneal and systemic chemotherapy (NIPS). Yonemura et. al. [15] published the results of NIPS in 2012 with IP taxotere and cisplatin combined with systemic S-1. Ninety-six patients were enrolled, CC0 was achieved in 70% and 36,8% of patients had complete pathologic response [16]. Another trial examine the use of preoperative HIPEC without cytoreduction, 53 patients treated with 2 cycles of Laparoscopic neoadjuvant Hipec (doxatel plus cisplatin). A significant PCI decrease was observed, from a median PCI 14,2 to a median PCI 11,8 and the cytology changed from positive to negative in 68% of cases.

CRS and HIPEC

Peritoneal metastasis remains the most common type of local recurrence after gastric cancer and is associated with median survival pf approximately 4 to 6 months [17]. On the other hand, the response rate to systemic chemotherapy for peritoneal deposits is low, which puts into perspective the role of CRS/HIPEC for these patients. A complete cytoreduction is the main requirement to prolong survival. The CRS must be carried out in referral centers with experience in the selection of patients [18]. There is a luck of phase III trials and CRS/HIPEC is not yet the standard of care. A phase III randomized trial by Yang et. al. [19] evaluated 68 patients were randomized into CRS alone (n=34) versus CRS/HIPEC (n=34) with a median PCI in both groups, both groups had the same proportion of patients (58,8%) undergoing CCso/1. Median OS was 6,5 months in the CRS group versus 11 months in CRS/HIPEC group (p=0,046). Both groups had similar rates of serious adverse effects (11,7 %in CRS vs 14,7 % CRS/HIPEC, p=0,8). On subgroup analysis patients with metachronous PM had worse survival than those with synchronous PM. Our registry in Greece which compare metachronous vs synchronous PM from gastric cancer we don't found any significance difference between two groups concerning the OS [20]. Coccolini et. al. [21] performed a meta-analysis to evaluate the impact of CRS/HIPEC. Outcomes of 20 RCTS were evaluated which include 2145 patients (1152 surgery + IP chemotherapy vs 993 controls). CRS and HIPEC was shown to increase the 3-year survival rates as well as decrease in the overall recurrence rate. The main bias of this study is that the authors did not distinguish patients with locally advanced disease from those with peritoneal metastasis. In 2019 [22] published the propensity score study CYTO-CHIP comparing 180 patients treated with CRS and HIPEC versus 97 patients treated only CRS. The patients treated with HIPEC had better survival rates 18,8 months vs 12,1 months without mortality and morbidity differences. The most important questions concerning HIPEC in gastric cancer is the confusion between different centers concerning drugs, doses, duration, and the administration technique.

Palliative Treatment

Many patients with diffuse PM from gastric cancer can develop malignant ascites which decrease the quality of life of these patients. The last 5 years a new procedure has been described to improve the quality of life for patients with refractory ascites. Pressurized intraperitoneal chemotherapy (PIPAC) is a closed laparoscopic technique of chemotherapy administration. The drug is administered aerosolized by an injector at high pressure and achieves better penetration into the tissues [23]. The clinical response of the method in patients with gastric cancer was 91% [24]. There are ongoing trials evaluating the use of PIPAC as a neoadjuvant therapy.

Conclusion

Based on current evidence, the therapeutic benefit of CRS/HIPEC for treatment of PM from gastric cancer is difficult to refute. Only patients with low PCI (≤6) can benefit from this multimodal treatment. We need more randomize phase III studies concerning the loco regional treatments with IP chemotherapy (HIPEC, PIPAC, EPIC) for have the evidence to changing the therapeutic steps for the management of PM from gastric cancer.

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