



Current treatment strategies for patients with only peritoneal cytology positive stage IV gastric cancer

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Abstract

Gastric cancer (GC) is one of the most common malignancies worldwide and surgery remains the only potentially curative treatment option for it. Although a significant proportion of GC patients are found with distant metastases already at the initial diagnosis. Peritoneal dissemination is the most common site of metastases. Positive peritoneal cytology (Cy1) is associated with poor long-term outcomes; thus, these patients are considered as stage IV even if macroscopic carcinomatosis is absent. Currently, there is no clear evidence for the most optimal treatment for this distinct subpopulation of the stage IV cohort. Available strategies vary from palliative chemotherapy to upfront gastrectomy. This comprehensive review summarized current evidence of different treatment strategies for Cy1 GC including roles of surgery, systemic and intraperitoneal chemotherapy.

Key Words: Gastric cancer; Positive peritoneal cytology; Gastrectomy; Systemic chemotherapy; Intraperitoneal chemotherapy

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Core Tip: Positive peritoneal cytology (Cy1) is associated with poor long-term outcomes; thus, these patients are considered as stage IV even if macroscopic carcinomatosis is absent. The evidence for the most efficient treatment of these patients is conflicting. We herein review current knowledge and the outcomes of different approaches for Cy1 gastric cancers.

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INTRODUCTION

Gastric cancer (GC) remains an important health care issue as it is the fifth most common and the fourth most deadly cancer worldwide[1]. Surgery is the only potentially curative treatment option for it[2,3]. Although up to 30%-40% of GC patients already have distant metastases at the initial diagnosis and typically they are not candidates for radical surgery[4,5]. Peritoneal dissemination is the most common site of metastases[6]. Peritoneal lavage cytology at staging laparoscopy is the modern standard to detect peritoneal spread even before visible peritoneal carcinomatosis (PC) could be detected[7-9]. Positive cytology alone (Cy1) is a negative prognostic factor for recurrence and survival[10]; thus, it is defined as metastatic (M1) factor and Cy1 patients are considered as stage IV even in absence of macroscopic carcinomatosis.

Current clinical practice guidelines by the European Society for Medical Oncology (ESMO)[11] and National Comprehensive Cancer Network (NCCN) recommend palliative chemotherapy for Cy1 patients with a possibility for re-staging through treatment. Although, Japanese GC treatment guidelines distinguish Cy1 patients as a distinct subpopulation of the stage IV cohort and suggest considering neoadjuvant chemotherapy followed by D2 gastrectomy if other non-curative factors are absent [12]. Such discrepancies and a lack of standardization arise from the gap of current knowledge for the most efficient treatment of patients with only Cy1 stage IV GC. Therefore, this review aimed to summarize the current evidence for peritoneal dissemination in GC and various available treatment options for Cy1 stage IV patients.

MECHANISMS OF PERITONEAL DISSEMINATION IN GC

Patients with locally advanced [that penetrates subserosal connective tissue, serosa, or adjacent structures (T3 or T4) or more advanced N-stage] GC, unfavorable histological subtypes (diffuse type and/or signet ring cell component), or primary scirrhous type GC are at higher risk for peritoneal metastases[13,14]. The development of these metastases is a multistep process which includes: (1) Cancer cells detachment from the primary tumor; (2) Survival in the microenvironment of the peritoneal cavity; (3) Malignant cells attachment to peritoneal mesothelial cells and invasion through basement membrane; and (4) Tumor growth and the onset of neoangiogenesis[15]. However, not all free intraperitoneal cancer cells seed into the peritoneum and turn into PC nodes. Most of these cells die even after successful attachment to the peritoneum, because of the peritoneal-blood barrier[15]. Further, mesothelium, the innermost monolayer of the peritoneum, has some basic protective mechanism against the adhesion of exogenous cells[15]. PC develops only after some sub-population of free GC cells manage to penetrate the submesothelial space by producing specific growth factors and matrix metalloproteinases, which induce the contraction of mesothelial cells, exposing the submesothelial basement membrane[15]. The presence of free GC cells in the peritoneal cavity represents the initial stages of PC development, however, currently, there are no methods to determine at what exact stage this multistep process has been diagnosed. Thus, it remains unclear if the treatment concept for Cy1 patients should aim to treat the present peritoneal disease or should aim to prevent its further development. Because of such controversies, different strategies have been adopted for Cy1 GC worldwide (Figure 1).

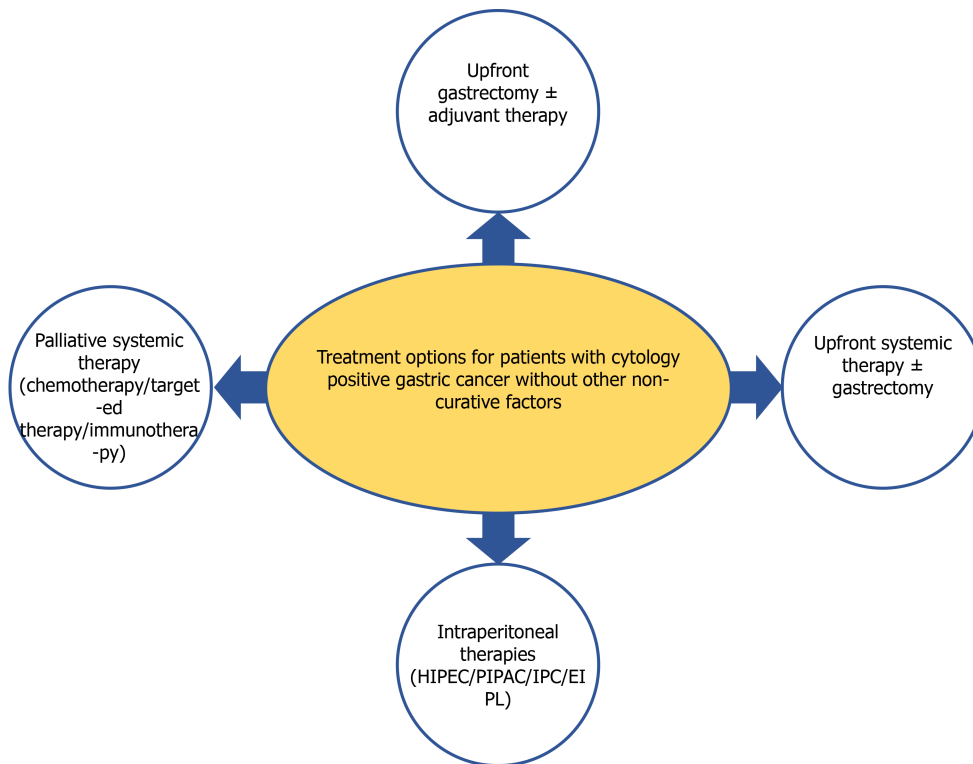


Figure 1 Different available treatment options for patients with cytology positive gastric cancer without other non-curative factors. HIPEC: Hyperthermic intraperitoneal chemotherapy; PIPAC: Pressurized intraperitoneal chemotherapy; IPC: Intraperitoneal chemotherapy; EIPL: Extensive peritoneal lavage.

UPFRONT SURGERY FOR CY1 GC PATIENTS

Surgery remains the only potentially curative treatment option for GC[3]. However, Cy1 represents stage IV disease, thus, despite it may be technically resectable, the biological rationale for surgery is controversial. The results of the randomized controlled trial (RCT) by the Japan Clinical Oncology Group (JCOG 0705) and Korea GC Association (KGCA01), comparing gastrectomy + chemotherapy *vs* chemotherapy alone in advanced GC with a single non-curative factor, showed no advantage of surgery for patients with PC[16,17]. Nonetheless, palliative chemotherapy is associated with disappointing long-term outcomes and Cy1 patients represent the distinct subpopulation of GC patients with peritoneal dissemination. Therefore, more aggressive treatment strategies including surgical resections are utilized for these patients in some centers.

Upfront radical gastrectomy followed by adjuvant S-1 monotherapy was investigated in a phase II single-arm (CCOG0301) study which enrolled 48 Cy1 GC patients across the multiple treatment centers in Japan[18]. Long-term follow-up showed 5-year overall (OS) and relapse-free survival rates were 26% and 21%, respectively. Peritoneal recurrence occurred in 62% of enrolled patients[18]. Similar results were confirmed by other groups from the East[19-21]. Kano *et al*[19] presented a retrospective study with a median follow-up of almost 10 years. Radical gastrectomy followed by adjuvant S-1 chemotherapy resulted in a 17.8% 5-year OS rate and peritoneal recurrence rate of 52.9%[19]. Further, the study documented the benefit of adjuvant S-1 monotherapy, as the median survival increased to 22.3 mo compared to 11.8 mo in the surgery alone group[19]. The benefit of adjuvant therapy was confirmed in another study from Korea by Shim *et al*[20]. Adjuvant chemotherapy by TS-1 ± cisplatin or oxaliplatin plus capecitabine (XELOX) or oxaliplatin + 5-FU (FOLFOX) improved median disease-free survival (DFS) (11.63 *vs* 6.98 mo, $P < 0.001$) and OS (25.50 *vs* 12.11 mo, $P < 0.001$)[20]. No significant differences were observed between the regimen of postoperative chemotherapy and survival[20], thus the most optimal regimen remains unclear. Another retrospective study by Komatsu *et al*[21] analyzed upfront gastrectomy followed by adjuvant S-1 based chemotherapy in 51 Cy1 GC patients, with a special focus on the impact of surgical radicality. Radical gastrectomy with ≥ D2 Lymphonodectomy was superior compared to palliative gastrectomy with the 5-year OS of 48.2% *vs* 18.2%, respectively[21]. Further, the impact of surgery for Cy1 GC treatment

was presented in another recent study from China[22]. Forty-eight Cy1 GC patients underwent upfront gastrectomy (75%; $n = 36$) or gastrectomy after neoadjuvant chemotherapy (25%; $n = 12$)[22]. The median OS and DFS were 22 and 16.5 mo, respectively[22]. However, the study did not provide a comparison of long-term outcomes between patients who received upfront surgery and neoadjuvant treatment [22]. In contrast, such a comparison was performed by Mezhir *et al*[23] In a Western cohort. Neoadjuvant therapy failed to improve DSS (1.7 *vs* 0.9, $P = 0.76$), although the relatively small sample size in the upfront surgery ($n = 29$) and neoadjuvant treatment groups ($n = 23$) should be taken into consideration[23].

Together, the current evidence indicates that radical upfront gastrectomy is feasible for Cy1 GC patients, and adjuvant chemotherapy is necessary to improve long-term outcomes. Although, most of the evidence for the upfront surgery arises from small-scale Eastern studies. Such treatment strategy needs further investigation in large-scale high-quality surgical trials, including the patients from Western parts of the world.

UPFRONT SYSTEMIC THERAPY FOR CY1 GC PATIENTS

As mentioned previously, Cy1 GC represents the stage IV disease, thus ESMO and NCCN guidelines suggest considering systemic treatment (chemotherapy) as it improves survival and quality of life compared to best supportive care[11]. Doublet or triplet platinum/fluoropyrimidine combinations \pm trastuzumab is recommended as a first-line palliative treatment[11]. Although there is no evidence for the most appropriate chemotherapy regimen to treat peritoneal metastases in GC[24], therefore, different schemes are adopted in clinical practice.

Several studies investigated the rates of conversion from positive to negative cytology following initial treatment by systemic chemotherapy[23-25]. The reported rates of conversion varied between 48.9% and 72.2% after treatment by various platinum/fluoropyrimidine combinations with or without docetaxel or trastuzumab [23-25]. Such conversion from positive to negative cytology results in improved oncological outcomes. Mezhir *et al*[23] showed increased disease-specific survival (2.5 *vs* 1.4 years) in those who converted to negative cytology. Similar, Yasufuku *et al*[25] and Aizawa *et al*[24] demonstrated improved 3-year (76.9% *vs* 10.5%) and 5-year (34.6% *vs* 17.6%) OS rates, respectively.

The high rate of conversions from positive to negative cytology and the clinical benefit of it proposes to consider the initial chemotherapy not as a palliative, but as neoadjuvant treatment. Further, the study by Badgwell *et al*[26] suggested, that palliative treatment may be inferior to neoadjuvant chemotherapy, despite only 41.6% of patients treated with it underwent surgery at some point of the treatment. Neoadjuvant therapy group showed a notably higher 3-year OS rate of 12% compared to 0% in patients who were considered as having incurable stage IV disease, therefore scheduled for palliative therapy only.

The upfront systemic therapy is the most promising when the conversion of cytological status is achieved, especially if converted patients can be allocated for further surgical treatment. The most effective chemotherapy regimens and the optimal number of cycles for conversions remain unknown, thus, future studies should elucidate these unclarities.

INTRAPERITONEAL THERAPIES FOR CY1 GC PATIENTS

As shown previously, systemic chemotherapy in a neoadjuvant or adjuvant setting plays an important role to improve Cy1 GC patients' outcomes. Although, systemic chemotherapy is considered to be limited efficacy for peritoneal dissemination because of the peritoneal-plasma barrier[27]. Therefore, direct intraperitoneal therapies have been suggested as a more effective alternative for these patients.

INTRAPERITONEAL CHEMOTHERAPY AND EXTENSIVE INTRAOPERATIVE PERITONEAL LAVAGE

The rationale for intraperitoneal chemotherapy (IPC) application is the possibility to achieve high local concentration while keeping the low systemic concentration of cytotoxic drug[28]. These pharmacokinetic features of the method increase the

therapeutic efficacy and decrease systemic toxicity. The possible limitation of IPC for the PC is the limited penetration of the drug. The maximum estimated depth of drug penetration is 3 to 5 mm, although actual penetration range from a few cell layers to a few millimeters[28]. Despite this shortcoming of the method for PC, it does not preclude the eradication of free intraperitoneal cancer cells. Thus, IPC was investigated as an attractive option for Cy1 GC patients.

Imano *et al*[29] conducted a pilot clinicopathological study to investigate intraperitoneal administration of 80 mg/m² paclitaxel at the end of the radical D2 gastrectomy for 10 Cy1 GC patients. Pharmacokinetic analysis showed that the peak plasma concentration of paclitaxel did not reach the cytotoxic threshold level of 0.1 mol/L, while intraperitoneal drug concentration was about 6773 folds higher[29]. Such IPC cleared the peritoneal cytology as no viable cancer cells were found at 24 and 48 h after IPC[29]. Following radical surgery with IPC majority of patients received adjuvant S1 based chemotherapy[29]. Long-term outcome analysis showed a promising 3-years survival rate of 56% and the peritoneal recurrence rate of 30%[29]. Further, the authors compared these survival outcomes with a historical cohort who received gastrectomy alone and concluded that IPC significantly improves the survival of Cy1 GC patients [29]. Another study on IPC for Cy1 GC investigated the additional benefit of extensive peritoneal lavage (EIPL)[30]. Shimada *et al*[30] study included 22 Cy1 GC patients who underwent: (1) Gastrectomy; (2) Gastrectomy + IPC with 100 mg cisplatin; or (3) Gastrectomy + IPC + EIPL by peritoneal cavity washing with 10 Liters of physiologic saline solution. Postoperatively all patients received adjuvant 5-FU based chemotherapy[30]. Long-term outcomes analysis showed 2-year OS rates of 0%, 14.3%, and 57.1% in groups 1, 2 and 3, respectively. Further EIPL reduced the peritoneal recurrence rate to 42.9% compared to 85.7% and 100% in gastrectomy + IPC and gastrectomy groups, respectively. Cancer cell detection analysis in the peritoneal lavage by reverse transcriptase-polymerase chain reaction (RT-PCR) suggested 10 Liters of physiologic saline as an optimal amount to flush out the free cancer cells from the peritoneal cavity[30]. Because of the promising results in the retrospective study, the gastrectomy + EIPL + IPC strategy was tested in the subsequent multicenter RCT [31]. The study included 88 Cy1 GC patients and randomly allocated them to three previously mentioned treatment strategies[31]. This prospective study confirmed the superiority of EIPL + IPC, as the 5-year OS increased to 43.8% compared to 4.6% and 0% in IPC and gastrectomy alone groups, respectively. Further EIPL + IPC significantly reduced the peritoneal recurrence rate to 40.0% compared to 79.3% in IPC and 89.7% in gastrectomy alone groups. After the promising results of the retrospective study were confirmed in the subsequent RCT, authors recommended considering EIPL-IPC therapy as a standard prophylactic strategy for peritoneal dissemination in Cy1 GC patients[31]. However, some conflicting data on the efficacy of EIPL was presented in a recent EXPEL study. This high-quality, open-label, multicentre, phase 3 surgical RCT, conducted at 22 hospitals from South Korea, China, Japan, Malaysia, Hong Kong, and Singapore enrolled 800 patients to evaluate the potential benefit of EIPL after upfront radical gastrectomy for cT3-4 GC[32]. However, EIPL by 10 Liters of saline did not improve 3-year OS [77.0% *vs* 76.7%; HR: 1.09 (95%CI: 0.78-1.52); *P* = 0.62], DFS [64.8% *vs* 69.4%; HR: 1.12 (95%CI: 0.86-1.47); *P* = 0.40], and 3-year cumulative incidence for peritoneal recurrence [7.9% *vs* 6.6%; HR: 1.33 (95%CI: 0.73-2.42); *P* = 0.35]. Moreover, EIPL was associated with higher risk of adverse events (RR = 1.58, *P* = 0.019)[32,33].

HYPERTHERMIC IPC

Hyperthermic IPC (HIPEC) is another available method for peritoneal malignancy. It combines the benefit of IPC with the potential advantages of hyperthermia. Experimental and clinical evidence indicates that hyperthermia at a range of 41 to 43 °C destroys malignant cells by selectively increasing the number of lysosomes and lysosomal enzyme activity in malignant cells leading to increased destructive capacity [28]. Also, hyperthermia decrease blood flow in most of the malignant tumors in contrast to the opposite effect in normal tissues[28]. Such effects, together with inhibition of oxidative metabolism in malignant cells promote cell death of the more sensitive malignant cells[28]. Further, heat promotes the cytotoxic effect of the chemotherapeutic agents [28]. Thus, HIPEC was widely investigated for peritoneal disease treatment including studies in Cy1 GC patients. Meta-analysis of randomized and high-quality non-randomized trials on HIPEC for prevention and treatment of peritoneal disease in GC patients found no difference in the 3-year OS (RR = 0.99, *P* =

0.85) for patients with PC[34]. Although, HIPEC obtained advantages in preventing peritoneal metastases (RR = 0.63; 95%CI: 0.45-0.88; $P < 0.01$) in high-risk patients, including Cy1 GC patients[34]. Also, HIPEC might be applied in a neoadjuvant setting as showed by Badgwell *et al*[35] in a single-arm phase II study. Nineteen stage IV GC patients only by positive cytology ($n = 6$) or limited PC ($n = 13$) received up to 5 cycles of neoadjuvant laparoscopic HIPEC after initial systemic chemotherapy. In total seven (36.8%) of these converted to negative cytology and no PC and 5 of them received radical gastrectomy[35]. It is important to emphasize that the conversion rate of 66.6% (4 of 6 patients) in Cy1 patients was considerably high[35]. This aggressive treatment resulted in a 3-year OS rate of 43.5%, and the median survival of patients who received gastrectomy was 29 mo. After encouraging results of the study Badgwell *et al*[36] conducted another single-arm phase II study for an even more aggressive approach. Twenty patients with limited PC ($n = 14$) or Cy1 ($n = 6$) were treated with initial systemic chemotherapy followed by 1-2 Laparoscopic HIPEC procedures and then subsequent gastrectomy with a cytoreduction and intraoperative HIPEC[36]. Such an aggressive treatment resulted in a 28% 3-year OS[36]. However, it is important to note, that subgroup of Cy1 patients had a very promising result of such treatment, as 50% ($n = 3$) of Cy1 were alive and recurrence-free at 32-49 mo after diagnosis. Despite the encouraging initial results on HIPEC for Cy1 patients, there is a lack of data from high-quality large-scale RCTs. Currently, an ongoing phase III GASTRICHIP trial[37] is designed to evaluate the effect of HIPEC in patients with a high risk of peritoneal recurrence, including Cy1 patients after neoadjuvant chemotherapy[37]. The long-term outcomes will be available in 2023 and the results will elucidate some unclarities regarding HIPEC's role for Cy1 GC patients[34].

PRESSURIZED IPC

Another new and emerging technique for a peritoneal disease is pressurized IPC (PIPAC). During PIPAC, laparoscopic access is obtained to create a pneumoperitoneum of 12 mmHg and nebulized chemotherapy is applied to create therapeutic capnoperitoneum for 30 min[38]. The rationale for PIPAC includes: (1) Optimization of drug distribution by applying an aerosol rather than a liquid solution; (2) Applying increased intraperitoneal hydrostatic pressure to increase drug penetration to the target; and (3) Limiting blood outflow during drug application[39,40]. Further, the minimally invasive approach of PIPAC allows multiple applications of the procedure and objective reassessment of the response through laparoscopy and biopsies[39]. Similar to laparoscopic HIPEC, PIPAC may be utilized in a neoadjuvant setting and also in combination with systemic therapy. Several retrospective and prospective phase II studies suggested that PIPAC may be a safe and promising option for GC patients with PC[41-44], although, there is a lack of data for its efficacy in a specific cohort of Cy1 patients.

SYSTEMIC CHEMOTHERAPY, TARGETED THERAPY, AND IMMUNOTHERAPY FOR CY1 GC PATIENTS

All above-mentioned treatment strategies could be considered as experimental, as the standard treatment option for M1 GC remains palliative systemic therapy[11]. Doublet or triplet platinum/fluoropyrimidine combinations are recommended for fit patients with M1 GC (including Cy1 patients) as standard conventional chemotherapy options [11]. Although, such treatment remains associated with poor outcomes[45], thus novel treatment options, like targeted therapy and immunotherapy, are of interest for these patients.

One of the available options, already included in a clinical practice guideline is trastuzumab - a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2). It induces antibody-dependent cellular cytotoxicity, inhibits HER2-mediated signaling, and prevents cleavage of the extracellular domain of HER2[46]. Large scale ToGA RCT showed that trastuzumab in combination with chemotherapy increases the survival of advanced or M1 HER2-positive GC patients[47]. A recent study showed trastuzumab deruxtecan, a humanized monoclonal anti-HER2 antibody attached to a cytotoxic topoisomerase I inhibitor through a cleavable linker is available and effective as a third-line treatment for HER2 positive GC patients[48]. Some other HER-2 targeting agents such as lapatinib, trastuzumab emtansine, pertuzumab are

also available, although their efficacy remains controversial[49_52]. Another available targeted therapy agent is ramucirumab, a fully humanized monoclonal antibody against vascular endothelial growth factor receptor 2[53]. This angiogenesis inhibitor was included in treatment guidelines as a second-line treatment option for patients with M1 GC after encouraging results of the REGARD and RAINBOW studies[54,55].

Another novel and promising drug class for M1 GC is immune checkpoint inhibitors. Some of these drugs improve antitumor T-cell activity by inhibiting immune checkpoints such as the programmed death-1 receptor (PD-1) and programmed death-ligand 1 (PDL1). PD1 is expressed on the surface of activated T cells that regulate their proliferation and activation and PDL1 is a major ligand for PD-1 expressed in some cancers, including GC cells[56,57]. Nivolumab is one of the available immune checkpoint inhibitors recommended in combination with fluorouracil/capecitabine and oxaliplatin for M1 HER2 negative GC, including Cy1 patients as recent RCTs demonstrated its efficacy for the first[58] and further lines treatment [59]. Pembrolizumab is another immune checkpoint inhibitor with antitumor activity in patients with PD-L1 positive GC. A phase II KEYNOTE-059 study showed promising activity and manageable safety of pembrolizumab monotherapy as a third-line treatment[60]. Although, the phase III RCT (KEYNOTE-062) failed to show improved survival with pembrolizumab or pembrolizumab plus chemotherapy compared to chemotherapy alone in previously untreated GC[61].

Despite some promising results of novel targeted therapy and immunotherapy drugs for M1 GC, the exact benefit for a distinct cohort of Cy1 GC patients remains unclear, as none of the current studies investigated this distinct subpopulation. Further studies are needed, to elucidate, the potential of novel systemic therapies for these patients.

LIMITATIONS OF THE CURRENT KNOWLEDGE AND PERSPECTIVES FOR FUTURE RESEARCH

The knowledge provided by the current evidence has some limitations. First, most of the available studies are relatively small in sample size. Second, many different treatment strategies including upfront gastrectomy, surgery after neoadjuvant systemic therapy, and IPC have been described for Cy1 GC, however, there is a lack of studies that would have compared them with each other. Thus, further large-scale international cohort studies comparing different treatments are needed to establish the most promising options. After, these should be tested in subsequent multi-center randomized control trials to provide robust evidence on the most efficient treatment for Cy1 patients.

CONCLUSION

Positive peritoneal cytology is associated with poor long-term outcomes in GC patients. Although, current evidence indicates, that this distinct subpopulation of the stage IV cohort may benefit from more aggressive treatment than palliative chemotherapy. Available strategies include upfront gastrectomy followed by adjuvant therapy, neoadjuvant chemotherapy option, and different methods of IPC utilization. Although, the most optimal treatment remains unclear because there is a lack of comparative studies. Thus, further clinical trials are needed to establish the best treatment option for Cy1 GC.

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