CANCER DIAGNOSIS & PROGNOSIS
3: 9-16 (2023) doi: 10.21873/cdp.10173

*Review*

# Indications, Safety, Efficacy and Survival Benefit of Intraperitoneal Chemotherapy in Patients With Advanced Gastric Cancer

AIKATERINI PARASKEVA[1], ALEXANDROS TRIANTAFYLLIDIS[2], MARIA KAZANTZI[1] and THEODOSIOS THEODOSOPOULOS[3]

*[1]Third Department of Surgery, "Evaggelismos" General Hospital, Athens, Greece;*
*[2]1st Surgical Department, NIMITS Hospital of Athens, Athens, Greece;*
*[3]Second Department of Surgery, "Aretaieion" General Hospital, National and Kapodistrian University of Athens, Athens, Greece*

**Abstract.** *Background/Aim: Advanced gastric cancer remains a significant concern for the medical community mostly due to the locoregional extension of the disease. Most commonly, stomach neoplasms are resectable, but not curable, due to the elevated percentage of peritoneal dissemination after gastrectomy and extensive lymph node dissection. Locoregional intraperitoneal chemotherapy plays a pivotal role in overall survival and prognosis of patients with advanced gastric cancer and shows a high probability of peritoneal dissemination after gastrectomy. In this review, we aimed to collect and present literature data concerning intraperitoneal chemotherapy in advanced stages of gastric cancer as well as evaluate the safety and survival benefit of the procedure. Materials and Methods: We conducted a survey including all randomized controlled trials and clinical trials that were published in the last 30 years. The keywords used were: advanced gastric cancer, intraperitoneal chemotherapy and peritoneal carcinomatosis. We searched for clinical trials in Pubmed, Embase databases and the Cochrane library. Inclusion criteria were: patients with advanced gastric cancer with no macroscopical signs of peritoneal dissemination, who were treated with D2 gastrectomy and received one or more cycles of intraperitoneal chemotherapy. The final review included 20 articles. Results: The safety of intraperitoneal chemotherapy, as well as the survival benefit of patients were evaluated. The majority of articles denoted that intraperitoneal chemotherapy is a safe procedure without severe or lethal complications. The majority of complications were hematological while non-hematologic complications were also noted. A survival benefit with statistically significant results ($p<0.05$) was observed in 6 out of 10 randomized controlled trials. Conclusion: Intraperitoneal chemotherapy for advanced gastric cancer is a safe procedure with promising results regarding survival benefit and prognosis. Further patient evaluation is required in order to standardize the type of chemotherapeutic agent and the sufficient dose and cycles for the most appropriate results.*

*Correspondence to:* Aikaterini Paraskeva, Third Department of Surgery, "Evaggelismos" General Hospital, Athens, Greece. Mob: +30 6975646749, e-mail: aikaterini.paraskeva93@gmail.com

*Key Words:* Advanced gastric cancer, intraperitoneal chemotherapy, peritoneal carcinomatosis, review.



Gastric cancer is one of the most aggressive gastrointestinal cancer types with unfavorable prognosis (1-3). Due to the unique shape of the stomach as well as its location, diagnosis is established at advanced stages, whilst worsening the prognosis and efficacy of therapy (1, 2).

Locally advanced gastric cancer and more specifically gastric cancer that infiltrates the serosa layer is responsible for peritoneal dissemination, an issue that concerns scientists in terms of choosing the right type of therapy and more specifically the surgical and oncological approach (4). Neo-adjuvant chemotherapy, surgery with total gastrectomy and D2 lymphadenectomy and adjuvant chemotherapy are the most frequently used lines of therapy in advanced gastric

cancer (2). However, the efficacy of these therapeutic plans, in advanced gastric cancer with regard to peritoneal dissemination, remains controversial and prognosis and survival rates are low.

Except for intravenous chemotherapy, intraperitoneal chemotherapy is as an alternative or complementary choice of therapy, especially for patients with peritoneal metastasis, because it is believed that higher concentration levels of the chemotherapeutic agents within the peritoneal cavity improves the effect of chemotherapy. In the same manner, it has been proposed that prophylactic intraperitoneal chemotherapy in advanced gastric cancer with high possibility of occult peritoneal dissemination, may result in better prognosis and may also prolong patient survival.

In this study, we aimed to evaluate the efficacy, safety, and survival benefit of intraperitoneal chemotherapy as an alternate or complementary therapy choice in patients with advanced gastric cancer with a high potential of peritoneal carcinomatosis.

## Materials and Methods

*Data sources, search strategy and selection criteria*. For the review process we followed the instructions of the Preferred Reporting Items for Systematic Reviews and Meta-analysis Statement (the PRISMA checklist 2020). Pubmed, Embase databases and the Cochrane library were used for searching articles, involving gastric cancer, peritoneal carcinomatosis and the role of intraperitoneal chemotherapy. Searching was focused on publications that were published during the last 30 years. Included participants were patients with advanced gastric cancer independent of sex or age. Interventions referred to intraperitoneal chemotherapy alone after gastrectomy or combination of intraperitoneal chemotherapy with systemic chemotherapy after gastrectomy. Patients being treated with hyperthermic intraperitoneal chemotherapy (HIPEC) or having established peritoneal carcinomatosis at the time of surgery were excluded. The group of comparison was either gastrectomy alone or combination of gastrectomy with systemic chemotherapy. The main outcomes were 1-, 2-, 3-, 4- and 5-year survival rates, as well as overall survival, disease-free survival, and safety. Finally, the study design referred only to randomized controlled trials and clinical trials.

The keywords used for database searching were: "intraperitoneal" AND "chemotherapy" AND ("stomach" OR "gastric") AND ("cancer" OR "carcinosis" OR "tumor" OR "carcinoma" OR "neoplasm") AND ("randomized controlled trials") AND ("clinical trials"). Only articles written in English language were included.

Studies were eligible for inclusion if the following criteria were met: Patients had advanced gastric cancer independent of age or sex, gastric cancer was adenocarcinoma histologically. All trials were randomized controlled trials and clinical trials that have been published in the last 30 years. In randomized controlled trials, the patients were divided into two groups: the intervention one that received surgery and intraperitoneal chemotherapy and the control group that received surgery alone or a combination of surgery with systemic chemotherapy. There was no obvious peritoneal dissemination or metastasis and the cytology after peritoneal lavage was negative for cancer cells. The study reported at least one of the following outcomes: 1-, 2-, 3-, 4- and 5-year survival rates, and/or overall survival, disease-free survival, and safety.

*Study selection*. The study selection procedure according to key words used resulted in 171 articles. According to title evaluation only, we excluded 135 articles. The number of articles finally included in the review was 36. It is worth mentioning that we excluded all papers that were using patients with established peritoneal carcinomatosis from gastric cancer and also all papers that were using HIPEC instead of conventional intraperitoneal chemotherapy. Additionally, we excluded all duplicates and all articles that had been published more than 30 years ago. In total 20 full text articles (5-24) were selected for this systematic review. The process of study selection procedure is illustrated in a flow chart (Figure 1), according to the PRISMA flow chart.

*Study characteristics*. In total, 1,843 patients with locally advanced gastric cancer were included in our review article (Table I). The mean patient age was 65 years and in general the percentage of male patients was greater than that of female patients. From all trials 11 were conducted in Japan, 1 in Korea (10), 1 in China (19), 4 in USA, and the remaining 2 in Turkey (9) and Austria (8), respectively. There was a diversity in the results section as different timeframes had been used for survival estimation (1-, 2-, 3-, 4- and 5-year survival rates) and also in some trials overall survival and disease-free survival had been used. Additionally, in almost all studies there was a description of adverse reactions by intraperitoneal chemotherapy. Five-year survival rates were evaluated in 5 studies, 3-year survival rates in 5 studies as well. There was an evaluation of 2-year survival rate in 4 studies and an evaluation of 1-, 2-, 3-, 4-, 5-year survival rates in 1 study (24). Only 2 studies evaluated the safety and adverse reactions of the intraperitoneal chemotherapy without reference to survival benefit (19). In the remaining studies there was a reference to overall survival and disease-free survival and almost all studies referred to overall survival as well. In terms of drug selection for intraperitoneal chemotherapy there was a variety of combinations of different drugs, such as cisplatin, mitomycin C, 5-FU, paclitaxel, raltitrexed, in different doses and different times of administration. Certain clinical trials used a combination of intraperitoneal chemotherapy with intravenous chemotherapy. Below, there is a table that describes the main characteristics of the eligible studies (7, 10, 11, 13, 14, 21, 23, 24).

## Results

*Limitations*. The main limitation of this review article was that most clinical trials included a small sample size, with the smallest one being n=9 (17), the largest n=521 (10), while the mean sample size value was n=48 patients. In addition, there was a considerable diversity regarding the drugs used for intraperitoneal chemotherapy. Each trial used a different therapeutic agent and thus comparison was difficult. Also, every study used therapeutic agents in different doses, different combinations, and different times. The time frame between surgical intervention and systematic chemotherapy was also different. Regarding the drug combinations, certain studies used a single therapeutic agent

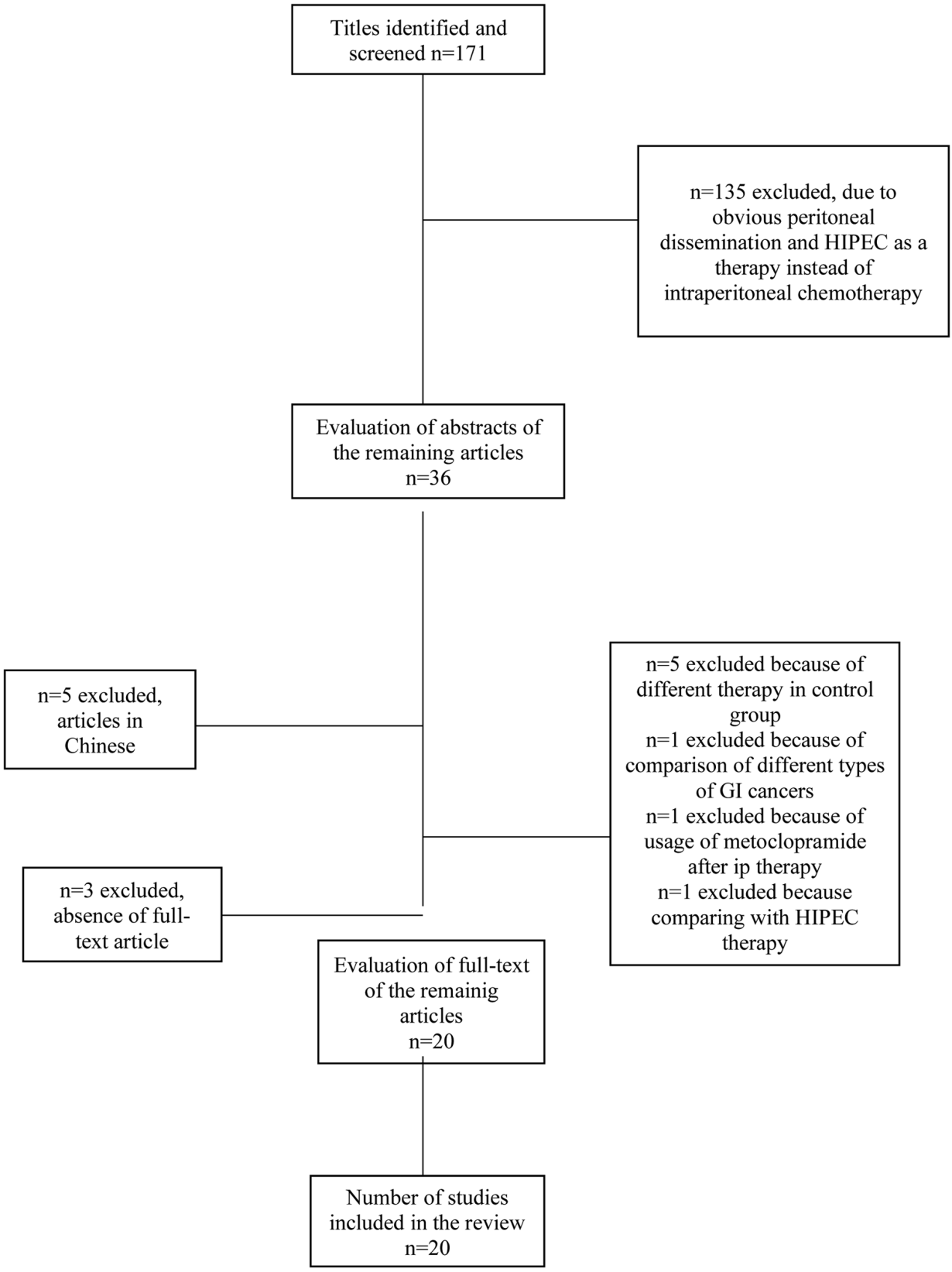


Figure 1. *Flow chart of the study selection process*.

Table I. *Articles included in the study.*

| Author (Ref.) | Publication year | Country | Sample size | Mean age (years) | Percentage of males (%) | Intervention | Follow-up (years) |
|---|---|---|---|---|---|---|---|
| Hagiwara *et al*. (21) | 1992 | Japan | 50 | 54.3 | 71.4 | Mitomycin C | 4.8 |
| Kelsen *et al*. (16) | 1996 | USA | 60 | 57 | 66.6 | Cisplatin<br>5-Flourouracil | 2 |
| Rosen *et al*. (8) | 1998 | Austria | 91 | Not mentioned | 67 | Mitomycin C<br>Activated carbon particles | 2.7 |
| Yu *et al*. (22) | 1998 | Korea<br>USA | 248 | 54.5 | 66.5 | Mitomycin C | 2.3<br>5-Fluorouracil |
| Shimoyama *et al*. (24) | 1999 | Japan | 46 | 58.3 | 75 | Mitomycin C | 3.9 |
| Yu *et al*. (14) | 2001 | Korea | 248 | 54.5 | 66.5 | Mitomycin C<br>5-Flourouracil | 2.3 |
| Topuz *et al*. (9) | 2002 | Turkey | 39 | 50 | 66.6 | Cisplatin<br>Mitoxantrone<br>5-Flourouracil<br>Folinic acid | 1.9 |
| Yano *et al*. (20) | 2004 | Japan | 25 | 61.1 | 60 | Mitomycin C<br>Cisplatin | |
| Newman *et al*. (15) | 2005 | USA | 34 | 58 | 64.7 | Cisplatin<br>Floxuridine | 2.3 |
| Brenner *et al*. (5) | 2005 | USA | 38 | 53 | 50 | Floxuridine<br>Leucovorin | 3.5 |
| Kuramoto *et al*. (11) | 2009 | Japan | 88 | 64.9 | 45.5 | Cisplatin | |
| Ishigami *et al*. (17) | 2009 | Japan | 9 | 64 | 55.5 | Paclitaxel | |
| Miyashiro *et al*. (23) | 2011 | Japan | 268 | 58 | 67.9 | Cisplatin | 6 |
| Imano *et al*. (13) | 2011 | Japan | 10 | 61 | 90 | Paclitaxel | 2.4 |
| Kang *et al*. (10) | 2013 | Korea | 521 | 56 | 68 | Cisplatin | 3 |
| Zhao *et al*. (19) | 2014 | China | 91 | 56.4 | 68.1 | Raltitrexed | Not mentioned |
| Peng *et al*. (6) | 2015 | Japan | 37 | 66 | 75.6 | Paclitaxel | 3 |
| Kodera *et al*. (12) | 2015 | Japan | 83 | 65.8 | 72.2 | Paclitaxel | Not mentioned |
| Shinkai *et al*. (18) | 2018 | Japan | 20 | 65 | 75 | Paclitaxel | 4.6 |
| Takahashi *et al*. (7) | 2018 | Japan | 86 | 66.2 | 72.2 | Paclitaxel | Not mentioned |

(6, 10-13, 17-19, 21-24) while others used a combination of two or more (5, 8, 9, 14-16, 20, 22). In the majority of eligible clinical trials patients received intraperitoneal chemotherapy in combination with systemic chemotherapy, which was intravenous or oral chemotherapy. Furthermore, certain studies evaluated only one cycle of intraperitoneal chemotherapy (5-8, 10, 13, 18, 19, 21, 22, 24) while others evaluated two or more cycles (9, 12, 14-17, 20, 23). In clinical trials, where a control group was absent, there was only a reference to survival benefit without comparison with previous studies or therapies that had been used in the past as a standard of care procedure.

Table II. *Adverse reactions after intraperitoneal chemotherapy.*

| Hematologic | Non-hematologic | Related to surgery |
|---|---|---|
| Leucopenia | Nausea | Abdominal pain |
| Neutropenia | Vomiting | Postoperative ileus |
| Febrile neutropenia | Diarrhea | Anastomotic leakage |
| Thrombocytopenia | Stomatitis | Pancreatic fistula |
| | Anorexia | Intrabdominal abscess |
| | Fatigue | Peritonitis |
| | Weight loss | |
| | Elevated liver enzymes and bilirubin | |

*Safety, toxicity, and adverse reactions*. In general, all clinical trials reached the result that intraperitoneal chemotherapy is a safe procedure and can be administered in eligible patients without serious or life-threatening adverse reactions. The most commonly used agents were cisplatin, mitomycin C, 5-FU and paclitaxel whilst one study used a combination of cisplatin with floxuridine (15), one floxuridine with leucovorine (5), one cisplatin mitoxatrone 5-FU and folinic acid (9) and finally one raltitrexed alone (19). All drugs were deemed safe for intraperitoneal chemotherapy, although being administered at different doses. Adverse reactions and toxic effects were evaluated according to the National Cancer Institute Common

Table III. *Survival rate of gastric cancer patients included in randomized controlled trials.*

| Author (Ref.) | Survival rate | Intervention group (%) | Control group (%) | *p*-Value |
|---|---|---|---|---|
| Yu *et al*. (all stages) (14); | 5-year | 38.7 | 29.3 | 0.219 |
| Yu *et al*. (stage II-III) (14) | 5-year | 44 | 14.9 | **0.03** |
| Hagiwara *et al*. (21) | 3-year | 68.6 | 26.9 | **<0.005** |
| Imano *et al*. (13) | 2-year | 70 | 22.2 | **<0.01** |
| Kang *et al*. (10) | 3-year | 71 | 60 | **0.02** |
| Kuramoto *et al*. (11) | 5-year | 43.8 (EIPL-IPC) | 4.6 (IPC)<br>0 (surgery alone) | **<0.0001** |
| Miyashiro *et al*. (23) | 5-year | 62 | 60.9 | 0.482 |
| Rosen *et al*. (8) | Overall survival | 738 days | 554 days | 0.44 |
| Shimoyama *et al*. (24) | 1-year | 94 | 81 | 0.049 |
| | 2-year | 82 | 63 | |
| | 3-year | 82 | 56 | |
| | 4-year | 73 | 32 | |
| Takahashi *et al*. (7) | 2-year | 64.1 | 72.3 | 0.5731 |

EIPL-IPC: Extensive intraoperative peritoneal lavage followed by intraperitoneal chemotherapy. Statistically significant *p*-Values are shown in bold.

Terminology Criteria for Adverse Events (CTCAE). They were categorized into hematologic adverse reactions, non-hematological and related to surgery adverse reactions. Among the most common hematological adverse reactions were leucopenia and more specifically neutropenia, febrile neutropenia, anemia, and thrombocytopenia (Table II). The majority were assessed as grade 1 or 2 and some of them grade 3 or 4. Hospitalization was required in some cases using conservative therapy strategies. In non-hematologic adverse reactions researchers observed most commonly adverse effects related to the gastrointestinal tract. Most common were vomiting, diarrhea, abdominal pain, anorexia, and stomatitis (Table II). Other non-hematologic adverse reactions were fatigue, weight loss, elevated liver enzymes and elevated bilirubin (Table II). None of them were assessed as serious complications and the only reason for hospitalization was dehydration. Finally, complications related to surgery were observed, such as abdominal pain, postoperative ileus, anastomotic leakage, pancreatic fistula, intrabdominal abscess and peritonitis (Table II). In conclusion, all adverse reactions that were provoked by intraperitoneal chemotherapy, were characterized as reactions that can be observed in patients treated with systemic chemotherapy as well, such as intravenous or oral chemotherapy. Thus, intraperitoneal chemotherapy as a different method, cannot be characterized as more toxic than intravenous or oral chemotherapy.

*Survival*. The survival benefit of intraperitoneal chemotherapy is illustrated more clearly from the results of randomized control trials rather than clinical trials, due to the absence of a control group. From the 20 studies included in our article, 3 did not assess the survival benefit at all and focused only on the safety and adverse reactions of the methods used (12, 17, 19). From the remaining articles, 10 were randomized controlled trials and 7 were clinical trials. In randomized controlled trials there was a statistically significant benefit in survival rate between the intervention and control group with $p<0.05$, except for 3 studies (7, 8, 23) that showed a benefit in survival, but the results were not evaluated as statistically significant ($p>0.05$) (Table III). Clinical trials show that overall survival is characterized as favorable during the observation period of patients (Table IV). Studies also noticed that patients receiving intraperitoneal chemotherapy had no signs of peritoneal recurrence or peritoneal dissemination during the observation period. Additionally, during observation there was no patient loss because of local recurrence or peritoneal dissemination.

## Discussion

Gastric cancer refers to the uncontrolled proliferation of cancer cells from the gastric wall which is part of the gastrointestinal tract. The most common histologic type is adenocarcinoma of the stomach (25). Gastric cancer possesses the 5$^{th}$ place in terms of new cases diagnosed in 2020 worldwide, with a number that approximates almost 1,200,000 of new cases (26). Thus, approximately 5.6% of cancers diagnosed worldwide are gastric cancers (26). This is of great concern to the medical community not only due to its high incidence, but also due to its even higher mortality rates (possessing the 4$^{th}$ place in number of deaths from gastric cancer) (26). Approximately 770,000 (7.7%) deaths have been recorded in 2020 worldwide attributed to gastric cancer (26). Mortality shows a steady reduction in all different regions in the world the last decades, mainly because of more in-depth understanding of the pathophysiology of gastric cancer and

Table IV. *Survival rate of gastric cancer patients included in clinical trials*

| Author (Ref.) | Median follow-up (months) | Median overall survival (months) | Disease-free survival (months) |
|---|---|---|---|
| Kelsen *et al*. (16) | 28 | 15.3 | Not mentioned |
| Newman *et al*. (15) | 28 | 36.5 | Not mentioned |
| Peng *et al*. (6) | 36 | 78% | 75.2% |
| | 60 | 74.9% | 67.3% |
| Brenner *et al*. (5) | 43 | 30.3 | 30.3 |
| Shinkai *et al*. (18) | 36 | 90% | 85% |
| | 60 | 77.1% | 66.8% |
| Topuz *et al*. (9) | 23 | 19 | 12 |
| Yano *et al*. (20) | 28 | 24.4 | 21.5 |

also because of the even improved prevention programs. Nevertheless, gastric cancer is still clearly possessing a remarkable place in the number of deaths worldwide, giving more space in scientists to observe and improve the prognosis of the disease.

Moreover, advanced gastric cancer and more specifically stages III and IV, is challenging in terms of definite therapy. Despite the fact that advanced gastric cancer is resectable, the prognosis and disease-free survival rates remain low, mainly because of occult locoregional dissemination during surgery.

One crucial factor for the insisting low levels of patient prognosis is advanced gastric cancer is locoregional extension of the disease, more specifically, peritoneal dissemination. According to TNM staging, advanced gastric cancer refers to stages III and IV, where the tumor invades the muscular and serosa layer respectively (27). As a consequence, at these stages cancer cells can protrude freely into the peritoneal cavity, thus peritoneal dissemination is established (4, 28). It is also strongly believed, that manipulation of the stomach during gastrectomy and lymph node dissection in locally advanced gastric cancer, leads to peritoneal dissemination of free cancer cells (4, 28). Free cancer cells into the peritoneal cavity can establish one or more sites of peritoneal metastasis, an unfavorable outcome, with poor prognosis despite systemic therapy.

In order to deal with this problem, the surgical community is trying to find ways to diminish the percent of peritoneal dissemination after gastrectomy. This is where locoregional therapy and more specifically intraperitoneal chemotherapy takes place. Intraperitoneal chemotherapy refers to the procedure where a surgeon administers a chemotherapeutic agent directly into the peritoneal cavity. Peritoneal cavity is a poorly vascularized part of the human body, thus making systemic chemotherapy an ineffective way for treating peritoneal metastasis (29). The idea of locoregional intraperitoneal chemotherapy came into play after the observation of the well-known peritoneal-plasma barrier. More particularly, if we put a part of the peritoneum under the microscope, we can notice that is composed of a layer of mesothelial cells and an underlying extracellular matrix. The last one, known as submesothelial stroma, plays the role of the peritoneal-plasma barrier. With this barrier the concentration of a therapeutic agent administered systemically is in low levels, in subtherapeutic levels. On the other hand, this barrier is really important when a locoregional therapy is used. So, intraperitoneal chemotherapy can achieve high concentrations of a specific chemotherapeutic agent resulting in a more effective method for treating peritoneal metastasis (29).

The most well-established technique for intraperitoneal chemotherapy is conducted with the placement of an importable port device (30). This device is placed into the subcutaneous tissue of the abdominal wall and connects with the peritoneal cavity with a catheter that is usually placed into the Douglas space. Chemotherapeutic agents are dissolved in 500-1,000 ml of saline and then administered intraperitoneally. The most frequent complications include infection of the peritoneal cavity through the port device and chemic peritonitis and abdominal adhesions that some chemotherapeutic agents may cause (30).

Taxanes, such as paclitaxel (PTX) and docetaxel (DTX), are considered to be more appropriate for intraperitoneal administration. This is because their pharmaceutical characteristics (31). Since PTX and DTX are hydrophobic high molecular weight materials when used intraperitoneally have a great advantage (31). They gradually absorbed from the lymphatic stomata, so they remain much longer into the peritoneal cavity and interact with the cancer cells. Furthermore, they belong to the category of drugs that are not supposed to cause adhesions.

In this review, we aimed to assess the safety and efficacy profiles of intraperitoneal chemotherapy in gastric cancer at advanced stages. The trials included in our survey resulted in the conclusion that intraperitoneal chemotherapy is, in general, a safe procedure that can be used in patients with advanced gastric cancer in order to prevent peritoneal

dissemination. Furthermore, intraperitoneal chemotherapy seems to be beneficial after gastrectomy in patients with advanced gastric cancer. Despite the fact that in all trials a different chemotherapeutic agent was used, at different doses and at different time intervals, most of them conclude that intraperitoneal chemotherapy improves survival with statistically significant results. There were some results not statistically significant, but importantly the patient survival rate improved after intraperitoneal chemotherapy.

Advanced gastric cancer concerns surgeons and oncologists around the world in terms of unfavorable prognosis and survival rates. Despite the fact that advanced gastric cancer in many cases still remains a resectable tumor, peritoneal dissemination plays a crucial role towards unfavorable results and methods to reduce the percentage of peritoneal dissemination after gastrectomy are still in progress. Locoregional intraperitoneal chemotherapy seems to be a promising, sufficient, and safe procedure to diminish intraperitoneal metastasis and improve survival in patients with advanced gastric cancer.

## Conclusion

Advanced gastric cancer with high probability of peritoneal dissemination remains a medical challenge. Locoregional intraperitoneal chemotherapy seems to offer a significant survival benefit in patients with locally advanced disease. It is yet unclear, but it seems that the role of intraperitoneal chemotherapy may be supplementary to systematic intravenous chemotherapy. It is also important to improve the technique of the procedure and to minimize complications. Nevertheless, more survey needs to be conducted with similar chemotherapeutic agents, and in similar doses in order to create the most appropriate guidelines for patients with advanced gastric cancer and high chance of peritoneal dissemination.

## Conflicts of Interest

The Authors declare no conflicts of interest.

## Authors' Contributions

A.P and M.K performed the study selection, designed the materials and methods, and organized the results. A.P and A.T organized the discussion and conclusion sections. T.T supervised the project.

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*Received September 27, 2022*
*Revised October 31, 2022*
*Accepted November 15, 2022*