REVIEW | OPEN ACCESS

Medical Science

To Cite:
Muciek M, Kawka J, Baranowska A, Baranowska K, Czyżewski F, Filipek K, Mrugała S, Mrugała W, Skierkowski B, Zalewska N. The effectiveness of surgical treatment with perioperative therapy compared to surgery alone in the treatment of gastric cancer - a systematic review. *Medical Science* 2025; 29: e3ms3471
doi: https://doi.org/10.54905/disssi.v29i155.e3ms3471

Authors' Affiliation:
[1]Medical Univeristy of Lublin, al. Racławickie 1, 20-059 Lublin, Poland
[2]Medical University of Warsaw, ul. Zwirki i Wigury 61, 02-091 Warsaw, Poland
[3]Szpital Miejski w Siemanowicach Śląskich, Poland
[4]Miedzyleski Specialist Hospital in Warsaw, Poland
[5]Medical University of Białystok, Jana Kilińskiego 1, 15-089 Białystok, Poland
[6]Bielański Hospital, Warsaw, Poland

*Corresponding Author
Medical Univeristy of Lublin, al. Racławickie 1, 20-059 Lublin, Poland
Email: michalmuc99@gmail.com

Contact List

Michał Muciek	michalmuc99@gmail.com
Jakub Kawka	jakub.kawka00@gmail.com
Alicja Baranowska	alicja.baranowska.priv@gmail.com
Katarzyna Baranowska	katarzynab508@gmail.com
Filip Czyżewski	czyzewskifilip@gmail.com
Kinga Filipek	kiniafilipek@icloud.com
Sebastian Mrugała	sebamrugala@gmail.com
Waldemar Mrugała	mrugalawaldek@gmail.com
Bartosz Skierkowski	skierabartek@gmail.com
Natalia Zalewska	natalia.zalewska2700@gmail.com

ORCID List

Michał Muciek	0009-0009-0657-0585
Jakub Kawka	0009-0003-7046-8127
Alicja Baranowska	0000-0002-0558-4194
Katarzyna Baranowska	0009-0001-9345-6626
Filip Czyżewski	0009-0006-8556-6565
Kinga Filipek	0009-0002-2758-4205
Sebastian Mrugała	0009-0007-7307-4114
Waldemar Mrugała	0009-0004-3853-0311
Bartosz Skierkowski	0009-0001-1353-4736
Natalia Zalewska	0009-0009-9411-0887

Peer-Review History
Received: 25 September 2024
Reviewed & Revised: 28/September/2024 to 30/December/2024
Accepted: 03 January 2025
Published: 09 January 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY
SCIENTIFIC SOCIETY

The effectiveness of surgical treatment with perioperative therapy compared to surgery alone in the treatment of gastric cancer - a systematic review

Michał Muciek[1*], Jakub Kawka[2], Alicja Baranowska[3], Katarzyna Baranowska[2], Filip Czyżewski[2], Kinga Filipek[4], Sebastian Mrugała[5], Waldemar Mrugała[1], Bartosz Skierkowski[1], Natalia Zalewska[6]

ABSTRACT

Introduction: Gastric cancer poses a significant challenge for physicians. This cancer is a growing concern globally due to its rising occurrence and high mortality rate. The standard approach to treatment has been surgery, but it often falls short of delivering effective outcomes. Combining surgery with perioperative chemotherapy could offer a promising alternative. In this article, we will analyze clinical studies comparing the aforementioned treatment methods. *Methodology:* We analyzed four independent clinical studies comparing surgery alone to surgery with perioperative chemotherapy. The total number of patients included in these studies was 2,841, who were randomly assigned to either the surgery-only group or the perioperative chemotherapy group (1,403 and 1,438 patients, respectively). *Results and discussion:* The overall five-year survival rate was 35 percent in the surgery-only group and 46.75 percent in the perioperative chemotherapy group. The five-year recurrence-free survival rate was 30 percent for the surgery-only group and 44 percent for the perioperative chemotherapy group. This indicates that perioperative chemotherapy increased overall survival by 33 percent and increased the proportion of patients with a five-year recurrence-free period by 46 percent. The clinical studies we reviewed clearly demonstrated the superiority of combining surgery with perioperative chemotherapy compared to surgery alone. Every effort should be made to refine chemotherapy or find alternative methods to support oncological surgery.

keywords: Gastric Cancer, Surgery, Chemotherapy

1. INTRODUCTION

Malignant gastric tumors represent a significant global health problem due to their prevalence and associated high mortality rate. Gastric cancer is influenced by numerous factors, both environmental and genetic (Machlowska et al., 2020). The traditional therapeutic approach involves surgical treatment, which is often insufficient, especially for advanced cancers. Despite significant advances in diagnostics and therapy, treating these malignancies remains a clinical challenge. In recent years, increasing attention has been given to the use of perioperative therapy as an adjunct to surgical treatment. The occurrence of malignant tumors in the stomach, gastroesophageal junction, and lower esophagus has declined in recent years.

Despite this, they remain a significant clinical concern and are still among the leading causes of cancer-related deaths worldwide. Gastric cancer ranks as the fifth most frequently diagnosed cancer and the fifth leading cause of cancer-related mortality globally (Ferlay et al., 2021). In 2018, there were 1,033,701 cases of gastric cancer, accounting for 5.7% of all cancers. It was the sixth most common and the second deadliest cancer that year. The incidence and consequent mortality from this cancer vary by region (with the highest number of cases in Asia and the lowest in Oceania) and gender (with approximately twice as many cases occurring in men) (Table 1).

Over 90% of patients are diagnosed after the age of 65. There is also a correlation between the incidence of gastric cancer and the Human Development Index (HDI); as the HDI increases, so does the incidence of malignant gastric tumors (Figure 1). In 2018, gastric cancer resulted in 782,685 deaths, with the highest number of deaths occurring in East Asia and the lowest in Oceania. The mortality rate for gastric cancer in 2018 was over 75% (Figure 2) (Khazaei et al., 2019). Given the high mortality rates and the limited effectiveness of surgery alone, the combination of surgical treatment with perioperative therapy has been proposed as a potentially more effective approach.

Objective

Our goal in this review is to analyze the efficency of surgical treatment combined with perioperative therapy compared to surgery alone for malignant gastric tumors. We will examine current scientific evidence that may support or contradict the use of perioperative treatment in the context of improving overall survival, surgical outcomes, quality of life, and reducing the incidence of postoperative complications. Through the synthesis of available data, our study seeks to offer a deeper insight into the role of perioperative therapy in the comprehensive treatment of gastrointestinal malignancies. Ultimately, this analysis may have significant clinical implications for therapeutic decision-making and improving treatment outcomes for patients with advanced gastric cancer.

2. METHODOLOGY

We analyzed four independent clinical studies comparing surgery alone to surgery with perioperative chemotherapy (Table 2). The total number of patients included in these studies was 2,841, who were randomly assigned to either the surgery-only group or the perioperative chemotherapy group (1,403 and 1,438 patients, respectively). Study duration was June to August 2024.

3. RESULT AND DISCUSSION

Epidemiology

The incidence of malignant tumors of the stomach, gastroesophageal junction, and lower esophagus has decreased in recent years. However, they remain a major clinical problem and they are considered as leading causes of cancer-related deaths across the world. Gastric cancer is the fifth most common and the fifth deadliest cancer globally (Ferlay et al., 2021). In 2018, there were 1,033,701 cases of gastric cancer, accounting for 5.7% of all cancers. It was the sixth most common and the second deadliest cancer that year.

The incidence and consequent mortality from this cancer vary by region (with the highest number of cases in Asia, where 769,728 new cases were diagnosed, and the lowest in Oceania, with 3,359 new cases) and gender (with approximately twice as many cases occurring in men) (Table 1). Over 90% of patients are diagnosed after the age of 65. There is also a correlation between the incidence of gastric cancer and the Human Development Index (HDI) (Figure 1). In 2018, gastric cancer resulted in 782,685 deaths. Similar to the incidence, the highest number of deaths occurred in East Asia (453,513), and the lowest in Oceania (2,119). Comparing the incidence of

gastric cancer to the number of deaths, the mortality rate for gastric cancer in 2018 can be estimated at over 75% (Figure 2) (Khazaei et al., 2019).

Risk factors

The diversity in the incidence of gastric cancer across different regions of the world results from human development and, most importantly, lifestyle, with diet being the critical component in the case of gastric cancer. A beneficial factor that reduces the risk of developing gastric cancer is the regular consumption of vegetables and fruits or the supplementation of substances found in them, as well as fiber. The predominant detrimental factor is a diet rich in starch, salt, red and processed meat, cheese, and butter (Bertuccio et al., 2013).

In addition to diet, other risk factors include alcohol consumption and smoking. However, the most significant risk factor, responsible for over 90% of gastric cancer cases, is infection with the microorganism Helicobacter pylori. H. pylori is a spiral-shaped, gram-negative, microaerophilic bacterium able to survive in an acidic environment. It colonizes the stomach lining, causing the most common bacterial infection worldwide. While the infection itself does not produce any symptoms, it serves as the basis for developing inflammation of the gastric mucosa, eventually leading to the formation of gastric ulcers and, ultimately, gastric cancer (Salvatori et al., 2023). Genetic factors are also significant in the risk of developing gastric cancer.

Table 1 Incidence of gastric cancer in various regions of the world.

Stomach cancer incidence worldwide divided by region in 2018			
Continent/Region	**Both Sexes**	**Female**	**Male**
Africa	31148	14123	17025
Northern Africa	7702	3184	4518
Southern Africa	2008	832	1176
Eastern Africa	9215	4643	4572
Western Africa	8080	3534	4546
Middle Africa	4143	1930	2213
America	96333	38963	57370
North America	29275	10787	18488
South America	50052	20332	29720
Central America	12881	6125	6756
Caribbean	4125	1719	2406
Asia	769728	244151	525577
Eastern Asia	619226	190928	428298
Western Asia	19655	7425	12230
Southern Asia	130847	45798	85049
Europe	133133	51522	81611
Northern Europe	11244	4131	7113
Southern Europe	29811	11535	18276
Central/Eastern Europe	64482	26055	38427
Western Europe	27596	9801	17795
Australia/New Zealand	3359	1188	2171
World	1033701	349947	683754

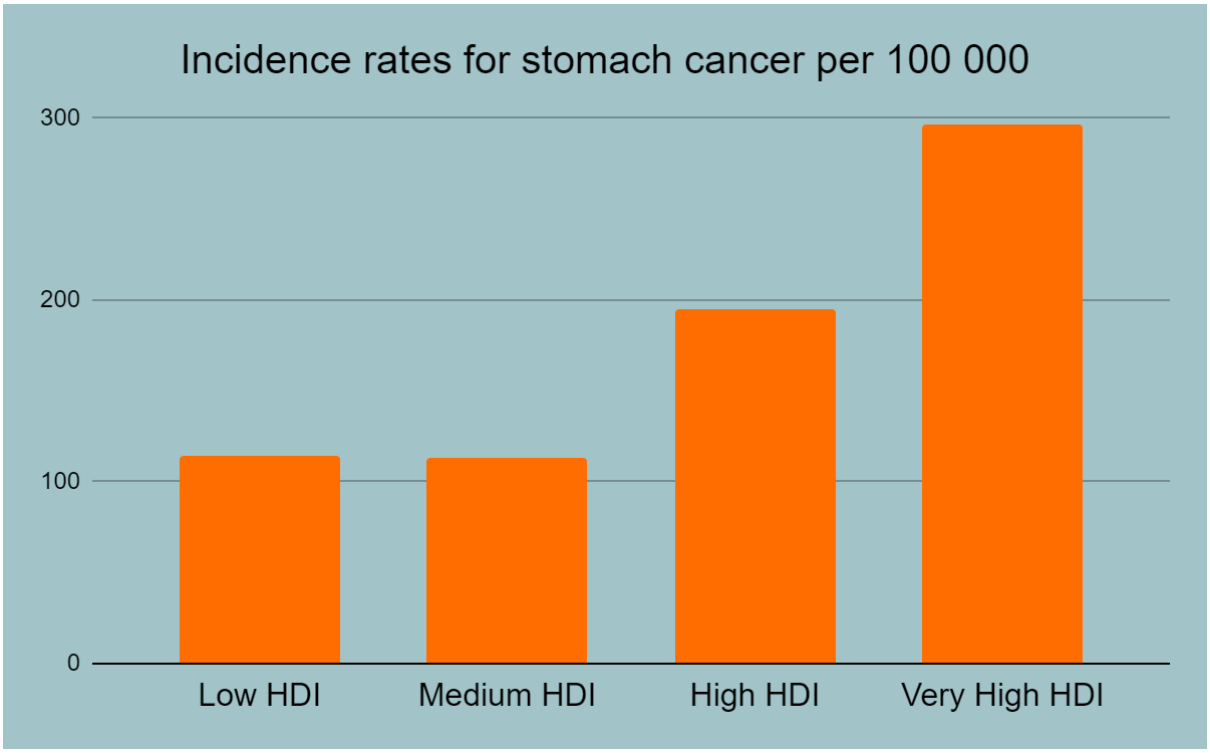

Figure 1 Incidence of gastric cancer depending on the Human Development Index (HDI).

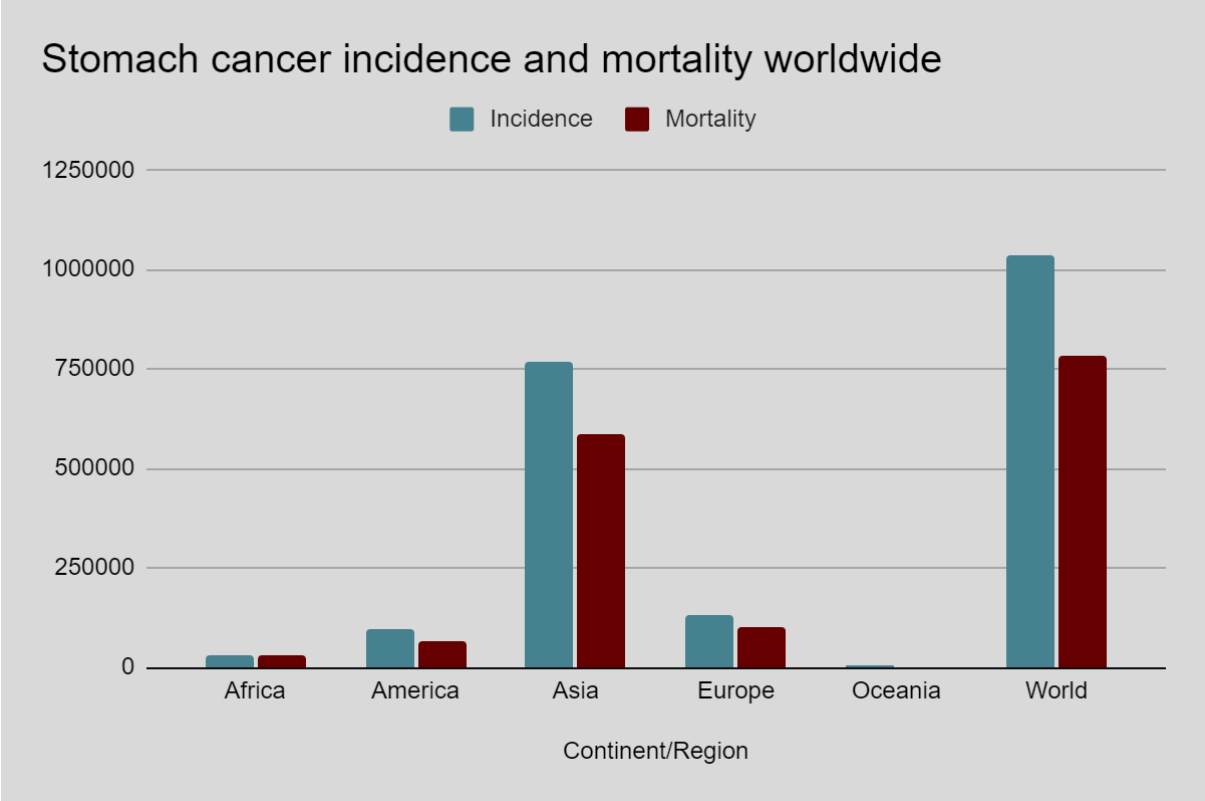

Figure 2 Incidence and mortality of gastric cancer in various regions of the world.

Treatment

The first approach to treating gastric cancer is surgical treatment (Tan, 2019). However, even after radical resection, the prognosis for this cancer remains poor. In recent years, increasing attention has been given to the use of perioperative therapy as an adjunct to surgical treatment. Perioperative therapy, encompassing chemotherapy, radiotherapy, and targeted treatments, is designed to shrink tumors, address micrometastases, and eliminate microthrombi. This strategy has the potential to improve surgical outcomes by minimizing the scope of surgery needed, boosting the likelihood of complete tumor removal, and promoting better postoperative functional recovery for patients. A key question remains: Do the advantages of perioperative therapy justify its side effects when considering its overall impact on enhancing patient quality of life and improving survival rate?

Surgical Treatment Alone vs. Surgical Treatment with Perioperative Chemotherapy

In the subsequent section of the article, we will analyze the results of clinical studies comparing the outcomes of surgical treatment alone versus surgical treatment with adjuvant and, or neoadjuvant therapy. Each study differs in the perioperative treatment regimens used. In the first study, published in The New England Journal of Medicine, a total of 1002 patients were enrolled (515 to surgery with accompanying perioperative therapy, 487 to surgery alone). Perioperative chemotherapy consisted of three cycles each of pre-and postoperative administration of epirubicin (50mg per square meter of body surface area) intravenously on the first day of the cycle, cisplatin at a dose of 60mg per square meter of body surface area intravenously with hydration also on the first day of the cycle, and fluorouracil (200 mg per square meter) for 21 days (one dose a day).

The combination of epirubicin, cisplatin, and continuous infusion of 5-fluorouracil (ECF) was described in a phase II study involving 139 patients, resulting in a response rate of 70% in advanced gastric cancer (Melcher et al., 1996). Warfarin at a dose of 1mg per day was given for thromboprophylaxis. Surgery was planned 3 to 6 weeks after completion of the third cycle of chemotherapy and 6 weeks after randomization for patients without chemotherapy. The rate of postoperative complications was similar in both groups. In the perioperative chemotherapy group, tumors were smaller and less advanced compared to the surgery-alone group. Over a 4-year follow-up period, 149 patients among the chemotherapy group and 170 in the surgery-alone group died. The overall survival rate was 36 percent among the chemotherapy group and 23 percent in the surgery-alone group.

The progression-free survival rates were 30 percent and 17 percent, respectively (Melcher et al., 1996; Cunningham et al., 2006). The next analyzed article describes a study conducted in Japan and published in the Journal of Clinical Oncology. A total of 1059 patients were enrolled (529 in the perioperative chemotherapy group, 530 in the surgery-alone group). Chemotherapy in the study involved the administration of S-1, divided into two daily doses based on body surface area (80, 100, or 120 mg). Neoadjuvant administration lasted for 4 weeks with a 2-week break before surgery, followed by postoperative administration a year after surgery. S-1 is a modern oral derivative of 5-FU, containing tegafur/gimeracil/uracil potassium in a molar ratio of 1.0:0.4:1. Tegafur (FT) is a prodrug of fluorouracil (5-FU), which slowly releases 5-FU in the body.

Gimeracil, a dihydropyrimidine dehydrogenase inhibitor, contributes to reduced 5-FU catabolism and significantly higher blood levels of 5-FU compared to FT alone. Oteracil potassium (Oxo), another enzyme inhibitor of 5-FU, may reduce gastrointestinal toxicity from FT. In theory, S-1 is better tolerated and more effective than 5-FU, making it more convenient for patients with advanced gastric cancer (AGC) (Yang et al., 2014). One hundred forty-five and 199 patients died, with 32 and 42 patients alive with recurrence, and 352 and 289 patients alive without recurrence, respectively, for the perioperative chemotherapy and surgery-alone groups (Yang et al., 2014; Sasako et al., 2011). In another study, which has been published by The New England Journal of Medicine, surgical treatment alone was compared with adjuvant chemoradiotherapy.

A total of 556 patients were enrolled, randomized to receive adjuvant chemoradiotherapy or surgical treatment alone (281 and 275 patients, respectively). Chemoradiotherapy consisted of fluorouracil at a dose of 400 mg per square meter of body surface area, leucovorin at a dose of 20 mg per square meter of body surface area, and radiotherapy at a dose of 4500cGy delivered at 180cGy per day for five days a week for five weeks. The combination of fluorouracil and leucovorin was highly effective in reducing the mass of gastric cancer tumors (Yang et al., 2014). The median follow-up time was 47 months, during which 328 patients (59 percent) died. The 5-year survival rates were 41 percent and 32 percent for the adjuvant therapy group and the surgery-alone group, respectively. The 5-year recurrence-free survival rates were 46 percent and 31 percent, respectively (Al-Batran et al., 2019; Macdonald et al., 2001).

The last article analyzed in our study has been published by the Journal of Clinical Oncology. It describes a clinical trial conducted in France. Although the study focuses more on the lower esophagus and gastroesophageal junction, some included patients had gastric

cancer, making it applicable to our review. The chemotherapy regimen in this study consisted of two or three preoperative cycles of fluorouracil at a dose of 800 milligrams per square meter of body surface area per day as a continuous infusion for five consecutive days and cisplatin (dose was 100 milligrams per square meter) of body surface area as a 1-hour infusion every 28 days. Similarly, 3 or 4 cycles of chemotherapy were administered postoperatively, totaling six cycles. The combination of fluorouracil and cisplatin increased the percentage of five-year survival in patients with gastric cancer (Li et al., 2015).

A total of 224 patients were enrolled, randomly assigned to either the surgical-alone group or the perioperative chemotherapy group, with 111 and 113 patients, respectively. Among these patients, 55 had gastric cancer. The analysis showed a five-year survival rate of 24 percent in the surgery-alone group and 38 percent in the perioperative chemotherapy group in comparison to the five-year recurrence-free survival rates were 19 percent and 34 percent, respectively (Ychou et al., 2011). Summarizing the above articles compared to the treatment of gastric cancer with surgical treatment alone versus surgical treatment with perioperative chemotherapy, a total of 2841 patients participated, with 1403 assigned to the surgery-alone group and 1438 to the perioperative chemotherapy group. Different chemotherapy regimens were proposed to patients in each of the studies.

Averaging the results of five-year survival and five-year recurrence-free periods in each of the described studies, we obtained favorable outcomes for the perioperative chemotherapy option. In the surgery-alone group, among 1403 patients, the five-year survival rate was 35.03 percent, while in the perioperative chemotherapy group, it was 46.75 percent. The five-year recurrence-free period in the surgery-alone group was 30 percent, whereas in the perioperative chemotherapy group, it reached 44 percent. This means that the use of perioperative chemotherapy in the treatment of gastric cancer increased the five-year survival rate by 33 percent and the five-year recurrence-free period by 46 percent. The data from the aforementioned clinical studies are summarized in (Table 2 and Figure 3).

Table 2 Analysis of data from clinical trials comparing the treatment of gastric cancer with or without perioperative chemotherapy.

			Surgery alone group			Chemotherapy group			
Clinical Trial/Article	**Authors**	**Patients in trial**	**Patients in group**	**progression -free survival**	**5-year survival**	**Patients in group**	**progression -free survival**	**5-year survival**	**Chemotherapy sheme**
Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer.	David Cunningham, William H Allum, Sally P Stenning, Jeremy N Thompson, Cornelis J H Van de Velde, Marianne Nicolson, J Howard Scarffe, Fiona J Lofts, Stephen J Falk, Timothy J Iveson, David B Smith, Ruth E Langley, Monica Verma, Simon Weeden, Yu Jo Chua, MAGIC Trial Participants	1002	487	18%	23.00%	515	31%	36.30%	three cycles neo-/adjuvant of 50mg/m2 epirubicin, cisplatin 60mg/m2 on 1st day and fluorouracil 200mg/m2 every day for 21 days + 1mg warfarin daily
Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer.	Mitsuru Sasako, Shinichi Sakuramoto, Hitoshi Katai, Taira Kinoshita, Hiroshi Furukawa, Toshiharu Yamaguchi, Atsushi Nashimoto, Masashi Fujii, Toshifusa Nakajima, Yasuo Ohashi	1059	530	53.10%	61.10%	529	65.40%	71.70%	4weeks before surgery, 1 year after S-1 twice a day in dose depending on body surface (80,100 or 120 mg)

Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction.	Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA	556	275	31%	32%	281	46%	41%	fluorouracil 425 mg/m2 + leucovorin 20mg/m2 5days a week for 5 weeks and radiotherapy 4500cGy in 5 weeks
Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial.	Marc Ychou, Valérie Boige, Jean-Pierre Pignon, Thierry Conroy, Olivier Bouché, Gilles Lebreton, Muriel Ducourtieux, Laurent Bedenne, Jean-Michel Fabre, Bernard Saint-Aubert, Jean Genève, Philippe Lasser, Philippe Rougier	224	111	19%	24%	113	34%	38%	2/3 neoadjuvant cycles and 3/4 (6 total) adjuvant cycles of fluorouracil 800mg/m2/d and cisplatin 100mg/m2
Summary	---	2841	1403	30%	35.03%	1438	44%	46.75%	---

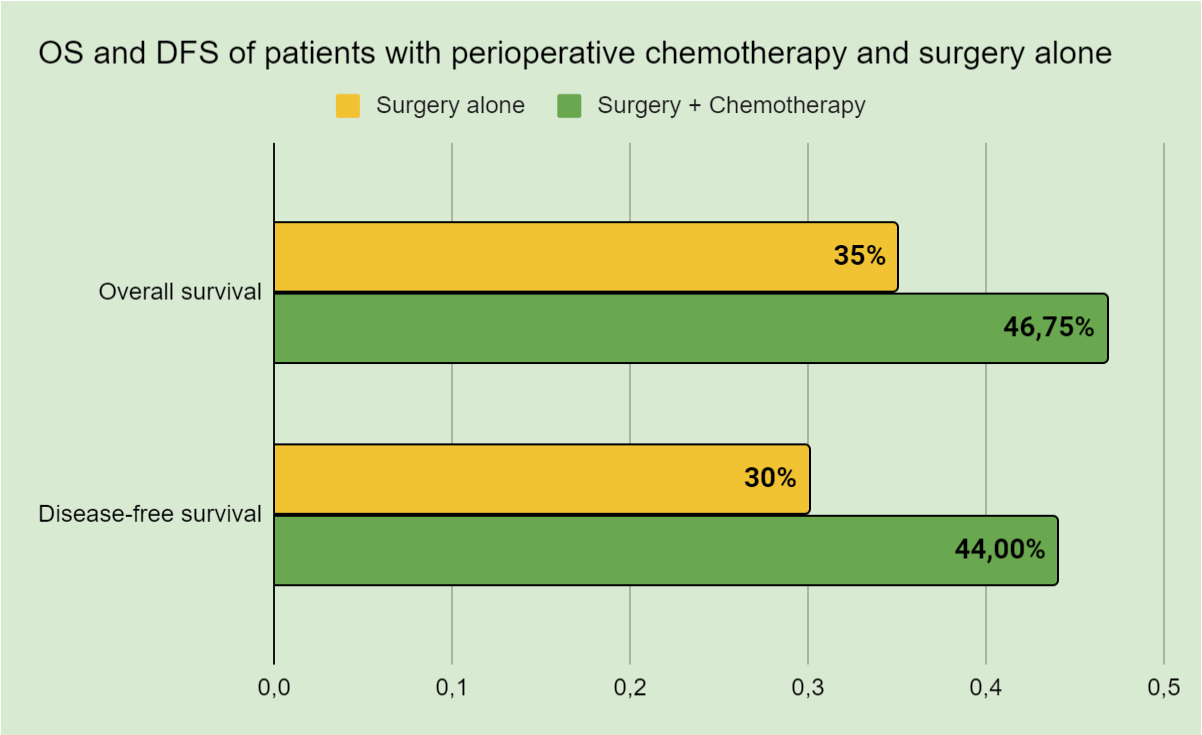

Figure 3 Comparison of 5-year survival and 5-year disease-free interval in patients undergoing perioperative surgery and patients undergoing surgery alone.

The optimal approach in treating gastric cancer, as well as many other malignancies, is surgery; however, relying solely on surgery often yields unsatisfactory results. Combining surgery with perioperative chemotherapy significantly increases patient survival,

prolongs disease-free intervals, and frequently reduces tumor mass, thereby reducing the extent of surgery required. Despite the many toxicities associated with chemotherapy, it aids in the radical surgical resection of the tumor, ultimately benefiting the patient.

4. CONCLUSION

Concluding our review, the use of perioperative chemotherapy in the treatment of gastric cancer can be considered a success; however, it is difficult to ignore the fact that the five-year survival rate does not even reach 50 percent. There is also a potential in targeted therapy research. Furthermore, novel immunotherapy approaches are under investigation, including immune checkpoint inhibitors, adoptive cell transfer, VEGF blockers, cancer vaccines, and CAR-T cell therapy. Unfortunately, at this moment, these therapies are still in the research stage and are not yet available as standard treatments for gastric cancer.

Acknowledgments
None.

Author's Contribution
Conceptualization: Michał Muciek, Jakub Kawka and Bartosz Skierkowski
Methodology: Michał Muciek, Alicja Baranowska, Katarzyna Baranowska, Filip Czyżewski
Software: Waldemar Mrugała, Sebastian Mrugała, Bartosz Skierkowski
Check: Michał Muciek, Jakub Kawka, Alicja Baranowska, Katarzyna Baranowska, Filip Czyżewski, Kinga Filipek, Natalia Zalewska
Formal analysis: Michał Muciek, Kinga Filipek, Natalia Zalewska
Investigation: Michał Muciek, Filip Czyżewski, Kinga Filipek
Resources: Michał Muciek, Filip Czyżewski, Natalia Zalewska
Data curation: Michał Muciek, Sebastian Mrugała
Writing - rough preparation: Michał Muciek, Waldemar Mrugała, Sebastian Mrugała, Bartosz Skierkowski, Alicja Baranowska, Katarzyna Baranowska, Jakub Kawka, Filip Czyżewski, Kinga Filipek, Natalia Zalewska
Writing - review and editing: Michał Muciek, Waldemar Mrugała, Sebastian Mrugała, Bartosz Skierkowski, Alicja Baranowska, Katarzyna Baranowska, Jakub Kawka, Filip Czyżewski, Kinga Filipek, Natalia Zalewska
Visualization: Waldemar Mrugała, Sebastian Mrugała
Supervision: Kinga Filipek, Alicja Baranowska, Katarzyna Baranowska, Filip Czyżewski
Project administration: Michał Muciek, Jakub Kawka, Waldemar Mrugała
All authors have read and agreed with the published version of the manuscript.

Funding
This study has not received any external funding.

Ethical approval
Not applicable.

Informed consent
Not applicable.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

REFERENCES

1. Al-Batran SE, Homann N, Pauligk C, Goetze TO, Meiler J, Kasper S, Kopp HG, Mayer F, Haag GM, Luley K, Lindig U, Schmiegel W, Pohl M, Stoehlmacher J, Folprecht G, Probst S, Prasnikar N, Fischbach W, Mahlberg R, Trojan J, Koenigsmann M, Martens UM, Thuss-Patience P, Egger M, Block A, Heinemann V, Illerhaus G, Moehler M, Schenk M, Kullmann F, Behringer DM, Heike M, Pink D, Teschendorf C, Löhr C, Bernhard H, Schuch G, Rethwisch V, von Weikersthal LF, Hartmann JT, Kneba M, Daum S, Schulmann K, Weniger J, Belle S, Gaiser T, Oduncu FS, Güntner M, Hozaeel W, Reichart A, Jäger E, Kraus T, Mönig S, Bechstein WO, Schuler M, Schmalenberg H, Hofheinz RD; FLOT4-AIO Investigators. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet 2019; 393(10184):1948-1957. doi: 10.1016/S0140-6736(18)32557-1
2. Bertuccio P, Rosato V, Andreano A, Ferraroni M, Decarli A, Edefonti V, La-Vecchia C. Dietary patterns and gastric cancer risk: a systematic review and meta-analysis. Ann Oncol 2013; 24(6):1450-8. doi: 10.1093/annonc/mdt108
3. Cunningham D, Allum WH, Stenning SP, Thompson JN, Van de Velde CJ, Nicolson M, Scarffe JH, Lofts FJ, Falk SJ, Iveson TJ, Smith DB, Langley RE, Verma M, Weeden S, Chua YJ, MAGIC Trial Participants. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med 2006; 355(1):11-20. doi: 10.1056/NEJMoa055531
4. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. Int J Cancer 2021. doi: 10.1002/ijc.33588
5. Khazaei Z, Mosavi JA, Momenabadi V, Ghorat F, Adineh HA, Sohrabivafa M, Goodarzi E. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide stomach cancers and their relationship with the human development index (HDI). WCRJ 2019; 6:e1257 doi: 10.32113/wcrj_20194_1257
6. Li YH, Qiu MZ, Xu JM, Sun GP, Lu HS, Liu YP, Zhong MZ, Zhang HL, Yu SY, Li W, Hu XH, Wang JJ, Cheng Y, Zhou JT, Guo ZQ, Guan ZG, Xu RH. S-1 plus cisplatin versus fluorouracil plus cisplatin in advanced gastric or gastro-esophageal junction adenocarcinoma patients: a pilot study. Oncotarget 2015; 6(33):35107-15. doi: 10.18632/oncotarget.5959
7. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, Haller DG, Ajani JA, Gunderson LL, Jessup JM, Martenson JA. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001; 345(10):725-30. doi: 10.1056/NEJMoa010187
8. Machlowska J, Baj J, Sitarz M, Maciejewski R, Sitarz R. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies. Int J Mol Sci 2020; 21(11):4012. doi: 10.3390/ijms21114012
9. Melcher AA, Mort D, Maughan TS. Epirubicin, cisplatin and continuous infusion 5-fluorouracil (ECF) as neoadjuvant chemotherapy in gastro-oesophageal cancer. Br J Cancer 1996; 74(10):1651-4. doi: 10.1038/bjc.1996.604
10. Salvatori S, Marafini I, Laudisi F, Monteleone G, Stolfi C. Helicobacter pylori and Gastric Cancer: Pathogenetic Mechanisms. Int J Mol Sci 2023; 24(3):2895. doi: 10.3390/ijms24032895
11. Sasako M, Sakuramoto S, Katai H, Kinoshita T, Furukawa H, Yamaguchi T, Nashimoto A, Fujii M, Nakajima T, Ohashi Y. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol 2011; 29(33):4387-93. doi: 10.1200/JCO.2011.36.5908
12. Tan Z. Recent Advances in the Surgical Treatment of Advanced Gastric Cancer: A Review. Med Sci Monit 2019; 25:3537-3541. doi: 10.12659/MSM.916475
13. Yang J, Zhou Y, Min K, Yao Q, Xu CN. S-1-based vs non-S-1-based chemotherapy in advanced gastric cancer: a meta-analysis. World J Gastroenterol 2014; 20(33):11886-93. doi: 10.3748/wjg.v20.i33.11886
14. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, Ducourtieux M, Bedenne L, Fabre JM, Saint-Aubert B, Genève J, Lasser P, Rougier P. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol 2011; 29(13):1715-21. doi: 10.1200/JCO.2010.33.0597