

The Relative Efficacies and Developments in Adjuvant and Neoadjuvant Therapy for Gastric Cancer - Review

Sami Ullah, Warda MohayUddin, Zafar Iqbal, Tong Dong and Wong Daorong*

Subei People's Hospital of Jiangsu Province (Clinical Medical College of Yang Zhou University), Yangzhou 225001, Jiangsu Province, China

*Corresponding author: Daorong Wang, PhD, MD, Department of Gastrointestinal Surgery, Subei People's Hospital of Jiangsu Province (The Clinical Medicine College of Yang Zhou Medical University), Yangzhou 225001, P. R. China, E-mail: daorong66@sina.com

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Abstract

This present study examined the efficacy and developments in gastric cancer modalities. This is in light of the fact that gastric cancer accounts for a significant number of cancer related cases reported across the world. Moreover, it is contented that curative treatment is still poor because modalities have been studied, but they have all been yielding controversial results. The study establishes that all modalities are effective and this rule out the popular claims that they are infective. Surgery has been lauded to be the most effective modality for control of the malignant cells at their early stages of growth. It is unfortunate that most patients are diagnosed when the malignant cells are at the advanced stage; the late diagnosis results in high rates of relapses. With early strategies to improve the treatment modalities having failed, a series of studies have been undertaken and significant improvements have been realized. However, these approaches have some limitations. The improvement of outcomes in the deployment of these modalities rests upon future developments to address the underlying inadequacies. The strategies of gastric cancer management are so dynamic and are reflected by the ongoing studies on how to manage and contain the cancer menace.

Keywords: Chemotherapy; Chemoradiotherapy; Gastric cancer; Neoadjuvant therapy; Surgery; Efficacy

Introduction

Gastric cancer accounts for a significant number of cancer related cases reported across the world [1]. It is contented that curative treatment is still poor [2]. For instance, curative treatments entail resection of the tumor, as well as lymphadenectomy, but these modalities are characterized by high rates of recurrences [3]. Both adjuvant and neoadjuvant modalities have been studied, but they have all been yielding controversial results [4]. However, it has also been worth acknowledging that a number of developments and studies aimed at managing gastric cancer spanning chemotherapy, radiation, and surgery tests are ongoing. It is intriguing whether these developments have yielded any results that are worth celebrating. The statistics infer that gastric cancer is ranked as the third common type of cancer worldwide (World Health Organization). The non-existence of screening strategies in the west results in the late diagnosis of gastric cancer in the west as compared to the Asian states. The late diagnosis is caused by the fact that gastric cancer has no specified symptoms at its early stages [5]. The prognosis of gastric cancer has not met the required standards despite the surgery and the timely lymphadenectomy. The five-year survival success of the early diagnosis is 75 percent, but at the late stages with the spread of cancer cells to lymph cells, the survival success is less than 30 percent. In the 1990s, neoadjuvant therapy was preferred in Europe for late diagnosis of gastric cancer.

The second phase studies found out resections R0 in comparison with the earlier trials improved the success rates [6]. There are merits of preoperative chemotherapy in comparison with surgery alone with success of R0 on patients subjected to neoadjuvant chemotherapy. The

effects of neoadjuvant chemotherapy did not yield long-term survival. The trials were lauded for the high survival rate compared with other trials undertaken in Europe [7].

From a pilot study conducted in Germany, it was inferred that there was increased positive impacts of radio chemotherapy on overall patient survival [8]. Perioperative chemotherapy is adopted as the standard care for gastric cancer patients in the west. In the Asian countries, patients are primarily subjected to a postoperative CT regimen that is orally administered. Randomized studies showed a significant improvement in survival rates as compared to surgery alone [9,10]. Notably, despite the various studies targeting the adjuvant CT in gastric cancer, the expected excellent results were not achieved in the studies conducted in the western region. Since the outcome of the INTO116 study were made public in 2001 MacDonald [11], the US have achieved success in the CRT, irrespective of the criticism over the inadequacy in lymphadenectomy. With the recent successful studies in Europe, perioperative CT has gained more recognition in the US and has been included as the treatment option for local gastric cancer in the current NCCN principles. The present study examines the relative efficacies and developments in adjuvant and neoadjuvant therapy for gastric cancer based on a review.

Methods

This study considers a number of documents and studies that need to be considered for the study. This review was conducted under PRISMA-P guidance. A search of literature was performed using Pub Med (MEDLINE) and EMBASE databases. Literature search was informed by the use of key words: chemotherapy, chemoradiotherapy, gastric cancer, neoadjuvant therapy, surgery, and efficacy which were formulated to ensure that only relevant sources are obtained. Studies were limited to humans and those published in English language

between 2005 and 2015. Headlines and abstracts were carefully read to exclude non-pertinent articles. If any doubt of suitability remained after the abstract was examined, the full manuscript was obtained.

Internet search engines were also used to perform a manual search for abstracts from international meetings which were then downloaded and studied (Table 1).

A meta search conducted on the relative efficacies and developments in adjuvant and neo-adjuvant therapy for gastric cancer based on systematic review	300
All the documents that included relevant information on relative efficacies and developments in adjuvant and neo-adjuvant therapy for gastric cancer based on systematic review	8
Documents that included relevant information on relative efficacies and developments in adjuvant and neo-adjuvant therapy for gastric cancer based on systematic review	4
A supplementary search for sources and evaluation reports detailing the relative efficacies and developments in adjuvant and neo-adjuvant therapy for gastric cancer based on systematic review	3
Number of documents that were included in the final review	20

Table 1: Manual search for abstracts from international meetings.

The first search of literature was conducted as a component of broad relative efficacies and developments in adjuvant and neo-adjuvant therapy for gastric cancer based on review. A supplementary study was further conducted as a way of ensuring that the material touching the subject was not misplaced. The analysis included analyzing the significance of the differences in observation and findings, and making an inference. For instance, in each case, the analysis would seek to understand what the number of sources that support certain positions is. Subsequently, the analysis would examine the significance in differences.

lesion sizes. Reduction of mass of lesions of tumors reduces the surgery invasiveness, thereby improving the abilities of discerning cancerous and normal tissues. Tumors initially considered non-operable because of indistinguishable margins can be treated with neoadjuvant chemotherapy as it creates an allowance for cancerous lesions to shrink and allow operations to be conducted. A number of studies have evidenced relative efficacies of neoadjuvant chemotherapy. The systematic review by Powell et al. [12] lauds the efficacy of neoadjuvant chemotherapy for the treatment of cancer. The findings are summarized in Table 2. As can be inferred, neoadjuvant chemotherapy is characterized by enhanced survival rate. A significant number of studies point to more than average survival rate.

Neoadjuvant/Perioperative Chemotherapy

Neoadjuvant chemotherapy describes a treatment done prior to surgical operations to extract tumors with the aim of reducing the

Author	Study location	Study	Treatment	No. Of patients	Median survival, mo	Survival rate, %
Cunningham [13]	United Kingdom	MAGIC	Pre/Postoperative ECF	250	4	5-yr SR, 36.3
			Surgery-only	253	20	23
Sasako [14]	Japan	ACTS-GC	S-1	229	-	5-yr SR, 71.7
			Surgery-only	530		61.6
Bang [15]	South Korea	CLASSIC	XELOX	520	46	3-yr SR, 83
			Surgery-only	515	25	58
MacDonald [11]	USA	SWOG 9009/INT 0116	5-FU/LV+RT	281	36	3-yr SR, 50
			Surgery-only	275	27	41

Table 2: Survival rate of neoadjuvant chemotherapy.

The study by Rivera, Gravalos et al. [16] sought to analyze the ongoing high-level empirical data underpinning the application of perioperative chemotherapy. The use of ionized radiation and anti-HER2 in adjuvant and neoadjuvant settings in facilitation of a clinical strategy set the application of the collected data on our institutional set guidelines for gastric cancer. According to the studies, the application of an array of models in determining when and the approach to be used for the treatment of gastric cancer is relatively efficient. Notably, the practitioners accept no defined standard of care. They

recommended the use of perioperative chemotherapy for managing resectable gastric cancer. In another study Jácome [17], sought to examine the significance of the use of 5-fluorouracil in reducing cases of relapses and overall improvement in the adjuvant chemotherapy process. The study acknowledges that the use of 5-fluorouracil in the chemotherapy process has been adopted in the vast western region. The toxins were reported by fewer than 10 percent of the patients subjected to D2 lymphadenectomy. Since the study findings were made public, the adjuvant therapy modalities have been enhanced to ensure

their safety and efficacy. Multiple modalities have been found to significantly reduce the relapse cases and the overall recovery process. The application of the D2 lymphadenectomy is that it can be administered in perioperative chemotherapy, adjuvant chemotherapy or neoadjuvant chemotherapy irrespective of the extent of lymphadenectomy. The analysis aimed at reporting the crucial advancements achieved in the recent years in the adjuvant therapies of gastric cancer and the approach of treatment based on the expertise of molecular biology of gastric cancer.

Adjuvant Chemotherapy

Adjuvant chemotherapy describes a therapy that entails chemotherapy, and is administered to supplement the initial or main therapy with the aim of maximizing its outcomes. However, even more intriguing has been whether this approach is effective. This review evidences positive outcomes in gastric cancer management with administration of adjuvant chemotherapy.

For instance, Miceli et al. [18], analyzed the empirical data and the shortcomings of adjuvant chemotherapy in the curative surgery for gastric cancer while underpinning the previous research and meta-analysis. The review highlighted the merits of adjuvant chemotherapy as compared to surgery. Moreover, the review recommends further research on the impact of economic factors, prognosis and the unmet needs of trials to compare the efficacy of chemotherapy with adjuvant treatment. Perhaps elaborate is the systematic review which lauds the efficacy of adjuvant chemotherapy for treatment of cancer.

Moreover, Schirren et al. [19], laud adjuvant chemotherapy as the only cure for regional gastric cancer. Therefore, it is crucial to meet the negative limit margin and to conduct successful lymph-node surgery. The limiting factor in the local diagnosis of gastric cancer is that patients are diagnosed when cancer has gone into its advanced stage. The reoccurrences of the tumor after the primary surgery aimed at curbing the disease is the result of poor prognosis. The above findings necessitated the new advancements of neoadjuvant diagnosis concepts. In the late 1980s, various patients were diagnosed with gastric cancer at its advanced stage and it was hard to undergo a perioperative, preoperative or postoperative surgery to enhance the prognosis surgery. However, this is not evidenced in other regions wherein other treatment modalities are popular.

Neoadjuvant/Perioperative Chemoradiotherapy

Neoadjuvant chemoradiotherapy describes a treatment including chemotherapy and radiotherapy done prior to surgical operations to extract tumors with the aim of reducing the lesion sizes. It has been thought that the reduction of mass of lesions of tumors reduces the surgery invasiveness, thereby improving the abilities of discerning cancerous and normal tissues [20].

According to Yasuhiro et al. [20], phase III trials that have sought to test the benefits of the post-operative adjuvant chemotherapies compared to surgeries have not evidenced a significant impact on survival, save for some cases of the studies that have been conducted in the US. Results on the studies conducted in Japanese contexts have pointed to moderate impact, especially pointing to the scenario that the use of oral fluoropyrimidines can effectively contain cancer that is less advanced. The study notes that Studies have since changed and now focus on neoadjuvant chemotherapies, in which phase II trials have also given promising results. Phase III trials that have sought to test the effectiveness of postoperative and preoperative chemotherapies have shown that these can enhance cancer among gastric cancer patients. Considering the rate of pathologic response is considered a crucial determinant of modality results, neoadjuvant chemoradiation approaches are also expected to increase pathological response. The systematic review by Reim, and Ebert et al. [21] lauds the efficacy of neoadjuvant chemoradiotherapy for the treatment of cancer. The findings are summarized in Table 3. In 2007 Susanne et al. [22] conducted a research to find out the efficacy of neoadjuvant chemotherapy especially in gastric cancer. The objective of the study was to analyze the effect of preoperative and postoperative chemotherapy using methotrexates, fluorouracil, and cyclophosphamides (MFC) and post-surgery chemotherapy verses post-surgery alone on sustainable prognosis. They focused on endocrine resistant malignant gastric cells. The study conducted a comparison between the preoperative and postoperative chemotherapy. In the first trial MFC as a treatment was utilized, while in the second study MFC was not utilized. The significance of neoadjuvant chemotherapy has been lauded over the traditionally adopted surgery strategies. Neoadjuvant chemotherapy is crucial in reducing and limiting the growth of the tumor. Neoadjuvant chemotherapy offers an option of surgery to the patient. The administration of the chemotherapy prior to surgery provides an opportunity to analyze the response of the cancer cells to the treatment. The initial objective of the study was to analyze the response of malignant gastric cells to chemotherapy. Further, they sought to find out if the administration of chemotherapy before surgery would affect the success of the treatment. They focused on patients with advanced gastric cancer. The previous studies concluded that surgery of the primary cancer cells affect the growth of the micro metastases. According to Susanne et al. [22], preoperative chemotherapy, using MFC, does not enhance the overall success in the patient's treatment. From the presented data, it can be inferred that there is an increased success rate in patients subjected to postoperative chemotherapy without the utilization of MFC. Recent studies of randomized attempts on three thousand nine hundred and forty-six patients concluded that preoperative chemotherapy and adjuvant chemotherapy are equivalently efficient in cancer treatment.

Author	Study and context	Timing	Sample	Results
Haller [23]	INT0116 United States	Adjuvant, chemoradiation	Surgery alone [n = 275] Surgery + 5-FU/LV/RT [n = 281]	Median OS: 27 mo HR = 1.35, 95%CI: 1.09-1.66
				[P = 0.005] Median OS: 36 mo
Park [2]	ARTIST	Adjuvant,	Surgery + 5-FU/LV/RT [n = 281]	3-yr DFS: 74.2%

	South Korea	chemoradiation	Surgery [D2 resection] + capecitabine/cisplatin [n = 228] Surgery [D2 resection] + capecitabine/cisplatin/RT [n = 230]	3-yr DFS: 78.2% [P = 0.08]
Sasako [14]	ACTS-GC Japan	Adjuvant, chemotherapy	Surgery alone [D2 resection] [n = 30] Surgery [D2 resection] + oral S-1 postop [n = 529]	5-yr OS: 61.1% 5-yr OS: 71.7 HR = 0.67, 95%CI: 0.54-0.83
Noh [24]	CLASSIC South Korea	Adjuvant, chemotherapy	Surgery alone [D2 resection] [n = 515] Surgery [D2 resection] + 8 cycles oral capecitabine + oxaliplatin [n = 520]	3-yr DFS: 74% [69%-79%] HR = 0.56, 95%CI: 0.44-0.72
Okines [25]	MAGIC United Kingdom	Perioperative, chemotherapy	Surgery alone [n = 253] 3 cycles ECF preop + surgery + 3 cycles ECF postop [n = 250]	5-yr OS: 23% 5-yr OS: 36% HR = 0.75, 95%CI: 0.60-0.93 [P = 0.009]
Ychou [7]	FNCLCC/FFCD France	Perioperative, chemotherapy	Surgery alone [n = 111] 5-FU/cisplatin preop + surgery + 5-FU/cisplatin postop [n = 113]	5-yr OS: 24% 5-yr OS: 38% HR = 0.69, 95%CI: 0.50-0.95 [P = 0.02]

Table 3: Summary trials of adjuvant chemotherapy and chemoradiotherapy.

Adjuvant Chemoradiotherapy

Adjuvant chemoradiotherapy describes a therapy that integrates chemotherapy and radiotherapy, and is administered to supplement the initial or main therapy with the aim of maximizing its outcomes. However, even more intriguing has been whether this approach is effective.

The study by Nicolas [26] analyzed secondary data of one hundred and sixty-eight patients with respect to effectiveness of adjuvant chemoradiotherapy. In forty-one months, median survival was reported. In twelve to seventeen weeks, median lapses were reported in the case study of surgery and the beginning of chemotherapy and radiotherapy.

Years	Author	Study location	Analyzed studies	Pooled HR (95% confidence interval)
1999	Earle et al. [28]	USA	13	0.80 (0.66-0.97)
2000	Mari et al. [29]	Italy	20	0.82 (0.75-0.89)
2001	Janunger et al. [30]	Sweden	21	0.84 (0.74-0.96)
2006	Oba et al. [1]	Japan	40	0.73 (0.60-0.89)
2008	Liu et al. [4]	China	19	0.85 (0.80-0.90)
2008	Zhao et al. [3]	China	15	0.90 (0.84-0.96)
2009	Sun et al. [27]	China	12	0.78 (0.71-0.85)

Table 4: Overall survival tendencies of adjuvant chemoradiotherapy compared to surgery alone.

Systematically, on the average of three and five years, survival was fifty-three and forty-one percent respectively. In 2009 Sun, Xiang and Chen [27] conducted a meta-analysis of survival tendencies of

adjuvant chemoradiotherapy compared to surgery alone based on previous studies. The study noted that adjuvant chemoradiotherapy was effective which are summarized in Table 4.

Marcus and Trevor [31] noted the challenge facing the diagnosis and treatment of gastric cancer was the non-existence of an internationally approved standard chemotherapy for advanced gastric cancer patients; in the US, this is before surgery cancer patients are subjected to adjuvant chemotherapy, and in Europe this is before and after the cancer surgery patients are subjected to intensive chemotherapy. Both the US and Europe patients are subjected to D1 dissections but to a limited extent. In the case of Korea, cancer patients are subjected to D2 resection. Such patients reported to be benefiting from postoperative adjuvant chemotherapy that is administered in the form of S-1. Alternatively, the patients can be subjected to oxaliplatin and capecitabine. As the first option therapy in palliative chemotherapy fluoropyrimidines, epirubicins, Irinotecans, the taxanes and platinum can be administered alone or in combination to treat the cancer patients. In the Asian states, fluoropyrimidines in the form of S-1 or capecitabine is administered orally and is the most proffered compared to the infusion of 5-fluorouracil. In the ongoing, standard chemotherapy for human cancer patients is integrated to counter the growth of gastric cancer cells.

MacKenzie [32] and the Gastrointestinal Cancer Disease Site Group (2011)sought to determine the optimal chemotherapy for gastric cancer in its advanced stages. The study came up with various recommendations, which included the following. They recommend the inclusion of a platinum agent to enhance the survival of patients undergoing chemotherapy treatment. The study further recommends oral administration of capecitabine as compared to intravenous 5-fluorouracil (5fu). According to MacDonald et al. [11] the course for gastric treatment is a dynamic one. They alludes that surgery is the only effective strategy for gastric cancer management. Especially with the large number of patients diagnosed with gastric cancer at an

advanced stage, surgery is the most recommended strategy. The late diagnosis is the result of relapses and poor treatment success. Studies have shown previous trials to enhance the treatment outcome bore little success. The recent randomized studies have concluded that postoperative and per-operative chemotherapy are the best treatment standards so far. It is worth noting the significant variance in the approach adopted between the east and the west. Asia reports the highest number of patients with advanced gastric cancer. The standard strategies adopted in Asian countries include extended surgery and adjuvant chemotherapy.

Stahl et al. [10] study focused on previous and present attempts to improve neoadjuvant chemotherapy. Gastric cancer is ranked as the second largest killer disease in the world. Surgery is the only strategy that provides a high success rate in the treatment process. In 2001, two significant trial results concluded that perioperative chemotherapy postoperative and chemoradiotherapy are the standard treatment strategies that guarantee success and high survival rates. The US cancer association has revised the malignant cells classification to include the lymph node in the gastric cancer cluster. The US cancer association and Wilke et al. [33] also highlighted the involvement of gastro-esophageal junction cancer cell growth. In the western countries, less lymph node surgery is the standard treatment approach. In the Asian countries, adequate surgery to the lymph nodes is considered as the standard treatment procedure. There is a remarkable success and survival rate between the west and the east, where the survival rates are significantly higher in the Asian countries. Studies have not been able to point out the reason behind the difference in the survival rate between the west and the east. Thus, this study recommends further studies to investigate the cause behind the difference in the success and survival rate in the west and the east [14,34].

Conclusion

In conclusion, this paper has sought to review the relative efficacies and developments in adjuvant and neoadjuvant chemotherapy and chemoradiotherapy for gastric cancer. The review points to relative efficacies of adjuvant and neoadjuvant chemotherapy and chemoradiotherapy, as far as gastric cancer management is concerned. This is contrary to claims of their ineffectiveness. However, this is not to say that these modalities do not have inadequacies. The improvement of outcomes in the deployment of these modalities rests upon future developments to address the underlying inadequacies. The strategies of gastric cancer management are so dynamic, reflected by the ongoing studies on how to manage and contain the cancer menace. Surgery has been lauded to be the most effective modality for control of the malignant cells at their early stages of growth. It is unfortunate that most patients are diagnosed when the malignant cells are at the advanced stage. Late diagnosis results in high rates of relapses. With early strategies to improve the treatment modalities, having failed, a series of studies have been undertaken and significant improvements have been realized. The studies facilitated the establishment of postoperative chemotherapy (INTO116) or perioperative chemotherapy. The perioperative chemotherapy is the standardized adjuvant therapy adopted in the western world. However, the standards in the treatment modalities differ between the western countries and the eastern countries. Asian countries experience the highest percentage of gastric cancer patients. The standard modality of treatment adopted in Asia is the resection modality, which is then followed by adjuvant chemotherapy. This review investigates the

previous and ongoing studies on the standardized adjuvant and neoadjuvant modalities to track the success in gastric cancer management and highlight areas of weakness in the present modalities to recommend further studies.

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