REVIEW

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LATEST PERSPECTIVES ON THE BENEFITS OF NEOADJUVANT THERAPY FOR PATIENTS WITH ADVANCED GASTRIC CANCER

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Summary

Treatment for gastric cancer has multiple approaches and options across the world. Standard treatment for the Asian population comprises D2-gastrectomy and adjuvant chemotherapy. However, in Europe and North America, clinical trials have shown that perioperative chemotherapy, given to patients before surgery, could improve resection and survival rates significantly. Most recent studies have also discussed the advantages of doublet *vs.* triplet chemotherapy regimens. Furthermore, researchers have been comparing the effects of perioperative chemoradiotherapy as opposed to chemotherapy alone. The specific advantages of previously stated therapy options, as well as any novel treatments, should be researched more thoroughly in the future.

KEYWORDS: *gastric cancer; screening; neoadjuvant therapy; docetaxel*

INTRODUCTION

Currently, gastric cancer is one of the most commonly diagnosed cancers worldwide. The occurrence and frequency of this diagnosis vary. First, it is more common in the male population than the female population, especially in developing countries. There is also a difference in incidence by region and culture; the incidence rates are highest in East and Central Asia and lowest in North America and Africa. There are multiple risk factors involved, such as chronic gastritis, H. pylori infection, obesity, diet, alcohol, and lower socioeconomic status. Consequently, the treatment varies. The curative treatment is surgery. However, earlier research has shown that, for a better outcome, a multidisciplinary approach is necessary. Therefore, the concept of neoadjuvant (preoperative) therapy has been included. In this review, the most current approaches and research on the benefits of multimodal treatment for the reduction of tumor size and better survival of patients with gastric cancer are summarized.

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DIAGNOSTICS AND STAGING

The symptoms of early-stage gastric cancer (GC) are usually non-existent or non-specific, and if not recognized in time, the cancer could progress to locoregionally advanced gastric cancer (LAGC). LAGC is defined as clinical T2 or higher stage disease with or without confirmed nodal involvement. Therefore, screening diagnostic procedures are the pathway to the best outcome and survival. Japan and South Korea are countries with ongoing, nationwide, organized GC screening programs. Screening includes certain tests that can detect specific types of cancer before signs or symptoms appear(1). The development of atro-

Table 1.
The 8th edition of the American Joint Committee on Cancer tumor-node-metastasis staging system for gastric cancer

Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)
TX primary tumor cannot be assesed	**Nx**: regional lymph node (s) cannot be assessed	**M0:** no distant metastases
T0 no evidence of primary tumor	**N0**: no regional nodal involvement	**M1**: distant metastases
Tis carcinoma in situ	**N1**: metastases in 1 to 2 regional lymph nodes	
T1a tumor invades the lamina propria and or muscularis mucosae	**N2**: metastases in 3 to 6 regional lymph nodes	
T1b tumor invades submucosa	**N3a**: metastases in 7 to 15 regional lymph nodes	
T2 tumor invades muscularis propria	**N3b**: metastases in more than 15 regional lymph nodes	
T3 tumor penetrates the subserosal connective tissue without invasion of the visceral peritoneum or adjacent structures		
T4a tumor invades the serosa (visceral peritoneum)		
T4b tumor invades adjacent structures		

phic gastritis is a precancerous stage. Therefore, screening for GC is achieved by measuring the markers of atrophy in the stomach, which include serum pepsinogens and serum ghrelin. Low levels of either marker could be associated with a higher risk of GC. Another method used for screening purposes is the detection of serum antibodies to H. pylori. The method is known as barium photofluorography, and it was first studied in Japan. In this study, the patient drinks a liquid that contains barium (a silver-white metallic compound), which coats the oesophagus and stomach as it is swallowed. A series of X-rays of the oesophagus and stomach are taken. This makes it possible to see the motion of the organs while exposing the patient to less radiation. The standard diagnostic procedure for detecting gastric cancer is endoscopy with a biopsy. Before making the decision of right therapeutic procedure and implementing any therapy, the staging of newly diagnosed gastric cancer is needed. The staging assesses the primary tumor invasion (T), lymph node involvement (N), and presence of distal metastasis (M) for every patient according to the American Joint Committee on Cancer TNM classification (Table 1). Current preoperative staging procedures include methods such as computed tomography (CT), endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), positron emission tomography (PET-CT), and laparoscopy(2). CT is usually the first choice because of its high accessibility and specificity. However, CT scans are often unable to show metastatic lesions smaller than 5 mm. It can also give incorrect information on the depth of the tumor invasion and lymph node metastasis. For this information, a better diagnostic procedure is EUS. EUS is most reliable for tumor depth invasion assessment, and it gives a more accurate evaluation of nodal invasion than CT. A fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (FDG-PET/CT) can be helpful in the preoperative staging of gastric cancer. FDG-PET/CT has better specificity but lower sensitivity in the detection of local lymph node involvement. The methods used less frequently and as alternatives to others are laparoscopy and MRI. They are mostly used for the diagnosis of peritoneal and other distant metastases. After this staging is completed, further treatment may begin.

CHOICE OF TREATEMENT

There are multiple types of treatment for patients with gastric cancer. After thorough analysis and specific staging, the right choice can be made. Accordingly, the treatment choice for stage 1 (T1N0M0 or T2N0M0) includes surgery followed by perioperative chemotherapy or postoperative chemoradiotherapy. Stages 2 and 3 (any T, any N, no M) are treated with surgery with preoperative (neoadjuvant) or postoperative (adjuvant) therapy. Lastly, stage 4 is a metastatic disease, so the therapy aims to control the cancer and maintain a good quality of life. Because of that, therapy can include surgery, chemotherapy, and radiotherapy. The role of radiotherapy is limited today (inadequate operation, D1 or R1).

SURGERY

The type of surgery (gastrectomy) depends on the site of the primary tumor, and it is important that the resection margin be kept at a minimum of 5 cm. Diffuse-type tumors located in the gastric body usually require total gastrectomy. Total gastrectomy is completed by restoring intestinal continuity, mostly by Roux-en-Y reconstruction. On the other hand, tumors of the gastric antrum require subtotal gastrectomy. In both cases, gastrectomy is followed by either D1 (perigastric lymph nodes) or D2 (perigastric and lymph nodes along the main arteries) lymphadenectomy(3).

ADJUVANT THERAPY

Based on the current evidence, postoperative (adjuvant) chemotherapy or chemoradiotherapy should be considered for patients with a higher stage of gastric cancer after operation (pT3 or T4pN0) or for those with pN+ and for R1 resection (microscopic residual cancer) or R2 resection (macroscopic residual cancer or M1)(3). The chemotherapy options for adjuvant treatment are fluoropyrimidine-based protocols: fluoropyrimidine (5-FU, S1, capecitabine) in combination with platinum drugs (cisplatin, oxaliplatin).

NEOADJUVANT CHEMOTHERAPY

Neoadjuvant chemotherapy (NACT) has been researched and included as a treatment option for stage 2, 3, and 4 gastric cancer since the 1990s. Since that time, a large number of studies and trials have defined the influence of NACT on the R0 resection rate and improvement in progress-free and overall survival of patients with gastric cancer. One of the first and most important trials was the MAGIC trial conducted in 2006(4). In this trial, a total of 503 patients from the UK and several other countries were included. Two groups of patients were formed: a group that was assigned to surgery alone and a group assigned to surgery and NACT with the ECF regimen (epirubicin, cisplatin, and 5-fluorouracil). The results showed that the second group had an increased R0 resection rate, decreased tumor size, and an improved overall survival rate. Another important study was the FFCD9703 trial conducted in France in 2007(5). In this trial, patients were divided into two groups: one getting surgery alone and the other receiving NACT before surgery. This FFCD9703 trial proved a statistically significant R0 resection rate and improved 5-year disease-free survival (DFS), which was in correlation with the results of the MAGIC trial. In 2010, the EORTC conducted another similar phase III trial(6). In this trial, a total of 144 patients with gastric cancer stages 3 and 4 were assigned to either surgery alone or surgery with NACT. NACT consisted of 48-day cycles of cisplatin followed by d-L-folinic acid and 5-FU (5-fluorouracil) given intravenously. The results of this trial proved an increased R0 resection rate and decreased tumor size. However, unlike MAGIC and FFCD9703, it failed to demonstrate a survival benefit. Also, postoperative complications were more frequent in the group receiving NACT. In recent times, the concept of NACT and the discoveries of older trials have been researched and expanded. The JCOG051 trial was published in 2020 by the Stomach Cancer Study Group (SCSG) of the Japan Clinical Oncology Group (JCOG)(7). Between 2005 and 2013, 316 patients with stage 3 and 4 gastric cancer were randomly assigned to either Arm A (distal gastrectomy with D3 lymphadenectomy) or Arm B (NACT with S-1 plus capecitabine). The primary endpoints were progression-free survival (PFS) and overall survival (OS). This phase III trial from 2010, as previously mentioned, proved that NACT had no significant impact on the improvement of PFS and OS. On the contrary, the 3-year OS was worse than double the duration of the trial. Because of that, the authors of this study believe that D2 surgery with adjuvant therapy should be the standard.

In the following year, 2021, an Italian single-center perspective was published(8). Previously mentioned trials were directed mostly to patients from Asia, so the aim of this trial was to prove the same hypothesis regarding NACT for European patients. From 2006 to 2020, 458 patients underwent either surgery alone or surgery with NACT (DOX protocol: docetaxel, oxaliplatin, and capecitabine). A significant difference in OS between the groups was found, with improvement in the group that received NACT. However, the PFS and recurrence rate did not differ significantly. Docetaxel-based chemotherapy was researched in another well-known European study. The main

goal was to compare two different NACT protocols. This FLOT4 study included 716 patients from 38 German hospitals with histologically confirmed T2 or higher resectable tumors and no evidence of distant metastasis proven(9). 360 patients were assigned to ECF (epirubicin, cisplatin, and 5-FU), and 356 patients were assigned to FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel). The group receiving FLOT showed improved OS compared to ECF, and the incidence of therapy related complications was similar in both groups. The FLOT trial was later studied more thoroughly and expanded as the FLOTA trial(10). The FLOTA trial collected data from patients with gastric cancer who received FLOT alone or FLOT with apatinib and underwent surgery at the Affiliated Cancer Hospitals of Zhengzou from 2017 to 2020. Apatinib is a multi-target tyrosine kinase inhibitor that inhibits the vascular endothelial growth factor receptor-2. Results showed that FLOT plus apatinib did not result in higher disease control rate (DCR), tumor regression (TRG), and ypTNM stages. However, a higher overall response rate (ORR) and improvement in the reduction degree of the target lesion diameter were found. This study offers confirmation that FLOTA could achieve better efficacy compared to FLOT alone, but it needs further research(9,10). Based on these positive findings for NACT in European and Chinese patients, a phase III PRODIGY study was conducted(11). The main objective was to investigate whether neoadjuvant docetaxel and oxaliplatin (DOC protocol) followed by surgery and S-1 adjuvant chemotherapy could improve the results of therapy in Korean patients with gastric cancer. Between 2012 and 2017, 266 patients, between the ages of 20 and 75 were randomly selected and underwent either surgery alone or surgery and NAT with the DOC protocol. Standard surgery was D2-gastrectomy, and both groups received S-1 adjuvant chemotherapy. The primary goal of this study was to find similarities in PFS and OS between the two groups. The final result showed improved PFS and significant tumor downsizing in patients assigned to both NACT and AT. Therefore, the PRODIGY trial suggests that the DOC protocol could be effective in Korean patients with stage 3 and 4 gastric cancer. From these previously summarized trials, it is evident that NACT could be used as either a doublet or triplet regimen. Generally, Asian guidelines endorse double regimens. However, the European Society for Medical Oncology (ESMO) and the National Comprehensive Cancer Network (NCCN) recommend triplet regimens. Because of that discrepancy, a group of Asian researchers conducted a retrospective cohort study aimed at comparing the efficacy and safety of the two different protocols(12). From 2013 to 2015, 140 patients were selected. 70 patients received a doublet regimen (fluorouracil and platinum), and the other 70 received the triplet regimen (docetaxel, platinum, and fluorouracil). The results of this cohort study concluded that the more intense triplet regimen did not significantly increase PFS or OS. Furthermore, post-surgery complications were more common in the triplet protocol.

NEOADJUVANT CHEMORADIOTHERAPY

Aside from the previously stated progression-free and overall survival as the primary objectives, newer trials have assessed the impact of NAT (neoadjuvant therapy) on pathological complete response (pCR). A retrospective cohort study was conducted using the NCDB (National Cancer Database), established by the American College of Surgeons and the Commission Center on Cancer(13). In this study, patients aged 18 or older who were diagnosed with GC between 2004 and 2016 were included. The hypothesis was that NAT could lead to pCR. The aim of the trial was to determine the factors regarding NAT that could lead to pCR and better survival. Results showed that neoadjuvant chemoradiotherapy, non-signet histology, tumor grade, and tumor location were the most significant factors leading to pCR. Because of that, the impact of NCRT was researched in other trials as well. One of the latest trials was published in 2021, and it included 3064 patients with gastric cancer diagnosed between 2004 and 2015(14). The patients were stratified into 9 treatment groups: neoadjuvant chemotherapy (nCT), neoadjuvant chemoradiation (nCRT), adjuvant chemotherapy (aCT), adjuvant chemoradiation (aCRT), neoadjuvant chemotherapy and adjuvant radiation (nCTaRT), chemotherapy with timing unknown (CTTU), chemoradiation therapy with timing unknown (CRTTU), radiation therapy with timing unknown (RTTU), and no perioperative therapy (NT). The primary endpoints were pCR and OS.

The final results of this study suggested that nCRT could lead to improved rates of pCR and survival compared to nCT alone. With the above results, these trials were in correlation with earlier trials on neoadjuvant chemoradiotherapy, such as INT0116 from 2001, RTOG from 2006, and the POET study from 2009(15-17). All of the above-mentioned studies showed that perioperative chemoradiotherapy could not only improve the R0 resection rate but also increase PFS and OS. Even though these studies had positive results on the use of perioperative chemoradiotherapy, the current National Cancer Institute (NCI) guidelines are based on the SWOG-9008 trial, which has an A1 level of evidence. SWOG-9008 was a prospective multi-institutional phase III trial that evaluated the effect of postoperative chemoradiation therapy versus surgery alone in 559 patients with completely resected stage IB to stage IV (M0) gastric cancer. After a 10-year follow-up, median survival was 35 months for the adjuvant chemoradiation therapy group and 27 months for the surgery-alone arm (P=0.0046). Median relapse-free survival was 27 months in the chemoradiation arm compared with 19 months in the surgery-alone arm (P<0.001). Based on these results, postoperative chemoradiation therapy may be considered for patients with stages II and III gastric cancer who have not received neoadjuvant therapy(18).

CONCLUSION

Based on the latest discoveries and research, it is stated that using perioperative therapy before gastrectomy can have a positive effect on the long-term outcome of patients with locally advanced gastric cancer. Most of these trials showed significantly improved R0 resection rates and decreased tumor size after combining NAT and surgery. However, opinions on its impact on PFS and OS differ. Some researchers believe that there is a significant improvement in both PFS and OS, but others disagree. However, most of them agree that docetaxel-based NACT could be the best choice for most patients. There are also opposing opinions on the type of NAT that should be used. Some trials showed that NCRT could have a bigger impact on the outcome than NCT. All of these opposite views could be a result of the limitations of each trial. The limitations mostly include small groups of patients involved, different staging techniques used, and diverse inclusion criteria implemented in some of the trials. Therefore, higher-quality trials with fewer limitations should be conducted to validate earlier assumptions on this topic.

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Sažetak

NAJNOVIJI STAVOVI O PREDNOSTIMA PRIMJENE NEOADJUVANTNE TERAPIJE KOD PACIJENATA S UZNAPREDOVALIM RAKOM ŽELUCA

T. Budija i J. Marić Brozić

Liječenje raka želuca ima više terapijskih pristupa i opcija diljem svijeta. Za azijsku populaciju standardna terapija uključuje D2 gastrektomiju s adjuvantnom kemoterapijom. Međutim, klinička ispitivanja u Europi i Sjevernoj Americi pokazala su da preoperativna kemoterapija, koja se daje pacijentima prije operacije, može značajno poboljšati R0 resekciju i stope preživljavanja. Najnovije studije također raspravljaju o prednostima dvostrukog naspram trostrukog režima kemoterapije. Nadalje, istraživači uspoređuju učinke preoperativne kemoradioterapije u odnosu na samu kemoterapiju. Specifične prednosti prethodno navedenih terapijskih opcija, kao i eventualni novi načini liječenja, trebalo bi detaljnije istražiti u budućnosti.

KLJUČNE RIJEČI: *rak želuca; screening; neoadjuvantna terapija; docetaksel*