



Surgeon's Neoadjuvant Therapy Approach in Gastric Cancer

Mide Kanserinde Cerrahin Neoadjuvan Tedaviye Yaklaşımı

Adem AKÇAKAYA

Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

Dear Readers,

I want to share with you, from a surgeon's point of view, the subject of recommending neoadjuvant treatment to patients with gastric cancer (GC), which is mostly obtained as a result of multidisciplinary meetings.

As is known, neoadjuvant therapy is the administration of therapeutic agents before the main therapy. Our main treatment for GC is surgery. In locally advanced gastric cancers, the standard treatment method is to administer neoadjuvant chemotherapy before surgery. The aim of neoadjuvant therapy is to facilitate surgery by reducing the primary mass, to test whether the tumor is sensitive to chemotherapy, and most importantly to contribute to survival. Neoadjuvant therapy reduces the tumor mass, allowing us to perform surgery without leaving any tumor behind. It facilitates the differentiation of cancerous tissue from normal tissue. With this, it can improve post-operative recovery and reduce the chance of cancer recurrence in the long run.

Despite advances in surgery and adjuvant therapy, local recurrence and distant metastasis are the main causes of death due GC. Increased R0 resection rates, prevention of local recurrence and distant metastases have become the main goal

of treatment, which has led to the development of neoadjuvant therapy in GC (1).

The reasons for performing neoadjuvant therapy in gastric surgery include the patient's higher tolerance to the chemotherapy administered before surgery, the increased chance of R0 resection and the possibility of obtaining a pathological complete response, the possibility to plan the postoperative regimen by seeing the pathological and biological response to the treatment, early treatment of micrometastases, and prevention of development of distant metastasis development in the early period. Also, theoretically, a higher potential effect can be obtained by administering drugs to the intact tumor bed after surgery (2,3).

According to The National Comprehensive Cancer Network (NCCN) guideline, neoadjuvant therapy is recommended for clinically $\geq T2$ tumors or node positivity (4). In patients with gastroesophageal junction (GEJ) stage II-III adenocarcinoma and GC, perioperative chemotherapy (CT) and combined neoadjuvant chemoradiotherapy (CTRT) have been shown to improve overall survival (OS) compared to surgery alone (2,5).

Many studies have been conducted to date in the treatment of gastric cancer. However, it is still controversial which neoadjuvant

Address for Correspondence: Adem AKÇAKAYA, Bezmialem Vakıf University Faculty of Medicine, Department of General Surgery, İstanbul, Turkey

E-mail: drakcakaya@yahoo.com **ORCID ID:** orcid.org/0000-0003-3116-7033

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therapy is best. I have mainly benefited from the publication of Dirikoç et al., which summarizes the medical oncology course of neoadjuvant therapy, and I thank the authors for their good work (2). With this article, I wanted to share the work done so far and finally my opinion as a surgeon.

One of the important steps is the MAGIC study. In this study, in which the perioperative ECF protocol was compared with surgery, the 5-year OS increased significantly (36% vs 23%, $p=0.009$, respectively) (5). In the subsequent EORTC 40954 study, no survival advantage could be demonstrated with the neoadjuvant 48-day cisplatin-fluorouracil regimen, and R0 resection rates were found to be higher only in the neoadjuvant treatment arm (7). In the French FNLCC-FFCD study, a statistically significant increase was observed in R0 resection rates, disease-free survival (DFS), and OS with the perioperative cisplatin-fluorouracil (CF) regimen in gastroesophageal junction tumors (8). In addition to neoadjuvant CT studies, the role of chemoradiotherapy was also investigated, and the primary goal in these studies was to increase pathological complete response (PCR) rates. In the phase 2 RTOG 9904 study, after 2 cycles of CF induction CT, infusional fluorouracil and weekly paclitaxel-guided CRT were administered, and a PCR rate of 26% and an R0 resection rate of 77% were achieved. The number of cycles of neoadjuvant therapy was another matter of debate, and an answer to this question was sought in the COMPASS study. In a 4-arm study consisting of 2 or 4 courses of S-1-cisplatin (SC) and paclitaxel-cisplatin (PC) regimens, PCR was obtained only in the combination arms and was independent of the agent. Different studies on neoadjuvant therapy in GC were conducted by the Japanese Clinical Oncology Group. In the phase 2, JCOG 0210 study, the efficacy of preoperative SC treatment in type 3 and type 4 GC was investigated and the mean survival was 17.3 months, while the 3-year survival rate was found to be 24.5%, and it was suggested that this combination could be effective and safe. In the JCOG 1002 study, the efficacy of preoperative docetaxel-cisplatin-S-1 treatment and adjuvant 1-year S-1 treatment were investigated in patients with extensive lymph node metastasis (ELM) who underwent D2 dissection and paraaortic lymph node dissection, and a response rate of 50% was obtained, which was inadequate (2).

The CROSS study compared long-term follow-up results of surgery alone and CRT combined with surgery. CRT combined with surgery was shown to have more significant OS benefits in patients with squamous cell carcinoma than in patients with GEJ adenocarcinoma (9).

Although local DFS was significantly increased with CRT in the POET study, no difference in OS was detected. In the results of

the TOPGEAR study, no difference was found between the CT and CRT arms in terms of toxicity and complications. In the CRITICS study, epirubicin-cisplatin or oxaliplatin capecitabine was used as CT, and a cisplatin-capecitabine regimen was applied with RT. At the end of the 61.4-month follow-up period, OS was found to be 43 months in the CT arm and 37 months in the CRT arm, with no additional contribution of adjuvant CRT. The effectiveness of targeted therapies in neoadjuvant therapy was investigated in two separate studies. In the ST03 study, bevacizumab was added to the perioperative treatment of gastroesophageal junction tumors, and the survival benefit of adding panitumumab was investigated in the NEOPECX study. Both studies showed no improvement in histological response or OS, but increased toxicity.

At the end of all these studies, when we came to 2019, the FLOT4 study, which would change our practice, was published and in this study, the Magic regimen and the FLOT (50mg/m² docetaxel, 85 mg/m² oxaliplatin, 200mg/m² leucovorin and 2600 mg/m² fluorouracil 24-hour infusion) protocol were compared and a 5-year OS contribution (36 months vs 23 months, respectively, $p<0.001$) was determined. For resectable GC or GEJ adenocarcinomas in the FLOT4 study, perioperative CT showed a significant OS benefit of docetaxel-based triple (fluorouracil plus leucovorin, oxaliplatin, and docetaxel) plus surgery compared to the ECF/ECX-MAGIC regimen. This study changed our point of view on neoadjuvant therapy, which we, surgeons, were previously skeptical of because of patients in whom treatment was previously unsuccessful or who relapsed with progression. In the end, perioperative FLOT treatment took its place as the first line recommendation in the NCCN guideline.

The efficacy of preoperative regimens containing S-1 was investigated in the PRODIGY and RESOLVE studies published in 2021. In the PRODIGY study, the addition of the neoadjuvant docetaxel oxaliplatin-S-1 regimen to the 1-year post-surgical adjuvant S-1 treatment improved DFS, while the RESOLVE study compared the adjuvant CapOx with the adjuvant and perioperative S-1-oxaliplatin (SOX) regimen. Perioperative SOX was superior to the adjuvant CapOx regimen based on 3-year DFS. The RESONANCE II study, which investigates how many cycles of the neoadjuvant SOX regimen should be administered, is ongoing (10). Following the positive results in the ToGA study of trastuzumab CT combination in Her-2 positive advanced GC, trastuzumab and other anti-Her-2 agents were also tested in neoadjuvant therapy, along with studies on the metastatic disease with other anti-Her-2 agents. The primary endpoint of the HER-FLOT study,

in which trastuzumab was applied in combination with the perioperative FLOT regimen, was reached, with a DFS of 42.5 months and a 3-year OS of 82.1% (11). In the PETRARCA study, it was observed that the addition of trastuzumab and pertuzumab to the perioperative FLOT regimen increased the rates of PCR (35% vs 12%, respectively, $p=0.02$) (12).

Immunotherapy was also brought to the agenda with the addition of pembrolizumab to perioperative CT in the Keynote-585 study. Studies are continuing in which the combination of another immunotherapy agent, camrelizumab, and a tyrosine kinase inhibitor, apatinib, and the combination of an antiVEGFR monoclonal antibody, ramucirumab, and FLOT are tested (13).

One area where we experience confusion as surgeons is gastroesophageal tumors. While the perioperative strategy to be applied in the treatment of GEJ cancer Siewert III and GC was more or less determined as we mentioned above, the questions regarding the ideal treatment of Siewert 1 and 2 cancers could not be fully answered. Some published meta-analyses have failed to clarify this dilemma. It is not easy to reach clear results due to patient characteristics and regional differences in surgical treatment (14,15). I think that the completion of studies in this area will allow surgeons to clarify their approach.

In conclusion, developments in neoadjuvant therapy and successful results have led us as surgeons to change our approach to GC. Better OS and DFS with neoadjuvant therapy, replacing the previous unsuccessful treatments, has increased the confidence in this approach. Neoadjuvant CT provides the opportunity to treat both the main tumor and invisible micrometastases, especially in tumors that have a high metastasis potential and have spread locally. Although there are some fuzzy points in patient and drug selection, treatment standards become clearer day by day after the FLOT 4 study. Another contribution that pleases us, the surgeons, is the increase in our R0 resection rates. The fact that the differences arising from the demographic characteristics of the patients, such as the location of the tumor and the type of tumor are overcome by immunotherapy and newly developed treatment models, seems to increase the usage area of neoadjuvant therapy even more.

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