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The Evolution of Neoadjuvant Therapy for Gastric Cancer: History, Current Situation, and Future Precision

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Abstract

Gastric cancer is one of the most common malignant tumors in the world. Gastric cancer continues to represent a major global health concern, with its high mortality rates and widespread incidence contributing to a significant disease burden across diverse populations, and China is also a high-risk area. With the continuous development of treatment methods and clinical trials, the symptoms of early gastric cancer are not easy to detect, and most patients are diagnosed at an advanced stage. Treatment options for distant metastasis are limited. Therefore, the 5-year survival rate of gastric cancer remains low. In recent years, there have been different research data on the efficacy of perioperative adjuvant chemotherapy and postoperative chemotherapy for gastric cancer. However, the results of a number of phase II clinical trials have confirmed that chemotherapy and neoadjuvant chemotherapy have the advantages of reducing tumor volume and clinical stage, thereby improving the R0 resection rate, which can improve the 5-year survival rate of patients to a certain extent. In particular, the effect can be further enhanced after combined immunotherapy and targeted therapy. This review synthesizes recent advancements in the application of neoadjuvant strategies for treating gastric cancer, focusing on their clinical efficacy and evolving therapeutic paradigms.

Keywords

Gastric Cancer, Neoadjuvant Therapy, Efficacy

1. Introduction

As reported by the International Agency for Research on Cancer (IARC) [1], WHO's cancer research agency, 2020 global estimates revealed 19.3 million new

cancer cases, with breast cancer surpassing lung cancer as the most diagnosed malignancy. Gastric cancer is the fifth most common cancer and the fourth leading cause of cancer-related deaths worldwide. In China, gastric cancer mortality rates per 100,000 population show significant gender disparity, with age-standardized rates reaching 22.8 in males compared to 9.5 in females. The overall national rate stands at 15.9, reflecting a higher disease burden in men. Surgical resection is the mainstay of treatment for gastric cancer, but studies have shown that even minor surgical trauma can affect several pathophysiological processes that may promote postoperative metastatic spread and tumor recurrence. Local effects include tumor seeding and wound-healing responses that can promote tumor cell migration, proliferation, differentiation, extracellular matrix remodeling, angiogenesis, and extravasation. Surgical manipulation of tumors can lead to the release of cancer cells into the blood circulation, which increases the probability [2] of distant metastasis of tumor cells. With the deepening of human research on tumor treatment, the treatment of gastric cancer has gradually developed from a single surgical resection treatment to chemical therapy (chemotherapy), radiation therapy (radiotherapy), molecular targeted drug therapy, immunotherapy, and other combined therapy methods. In this review, we discuss the research progress of neoadjuvant therapy for gastric cancer.

2. Methods for Staging Diagnosis of Gastric Cancer

2.1. The Synergistic Role of Multiple Imaging Techniques in Staging Gastric Cancer

In recent years, it has become the consensus [3] of international experts to use the constantly updated TNM staging as the core guidance for gastric cancer therapy. Clear and complete preoperative staging is the key to guiding clinicians in choosing treatment options. The mainstream diagnostic methods for preoperative staging of gastric cancer include endoscopic ultrasonography (EUS), multislice spiral computed tomography (MDCT), magnetic resonance imaging (MRI), positron emission computed tomography/X-ray computed tomography (PET/CT), and laparoscopic diagnostic exploration. These methods have their own suitable application scenarios in the diagnosis of TNM staging, and can provide the key information of pre-therapy staging in the evaluation of disease, and have become an indispensable part of the clinical application of neoadjuvant therapy.

2.2. Endoscopic Ultrasonography

EUS has the combined advantages of endoscopy and ultrasound and can more clearly determine the degree of tumor invasion, lymph node invasion, and adjacent organ involvement. MDCT can overcome some of the shortcomings of CT scans, provide higher quality image data, and can also be used for the diagnosis of distant metastasis and locoregional diseases. Ungureanu BS [4] *et al.* conducted a meta-analysis in 2021 to investigate the diagnostic accuracy of EUS, MDCT, and EUS + MDCT in TNM staging evaluation of 2047 gastric cancer patients and com-

pared the results of 12 studies. The results of the analysis showed that, compared with multi-slice spiral CT, EUS was superior to MDCT in preoperative T1 and N staging of gastric cancer, while MDCT had higher specificity than EUS in M staging. However, there was no significant difference in sensitivity between the two methods. It should be noted that the role of EUS in the diagnosis of distant lymph node metastasis is limited by the detection range of the ultrasound probe and the subjective factors of the operator.

2.3. Magnetic Resonance Imaging

MRI has a higher output resolution for soft tissue and avoids radiation-related side effects. The accuracy of MRI in assessing T staging was similar to or slightly better [5] than that of the most commonly used imaging modalities, that is, EUS and MDCT. The application of MRI is limited by its long examination time, susceptibility to respiratory motion artifacts, limited availability, and high cost, and it is not recommended as a routine method [6] by the current TNM staging guidelines, making MRI an alternative imaging modality when CT is contraindicated or when the results of CT are uncertain.

2.4. Positron Emission Computed Tomography/X-Ray Computed Tomography

PET/CT is a noninvasive imaging method that is significantly different from other anatomical imaging methods for gastric cancer examination. Although 18F-FDG PET/CT is widely used in oncology for the assessment of metastasis, it has not been routinely used in gastric cancer. Some studies [7] have shown that 18F-FDG PET/CT has obvious advantages over spiral CT in the diagnosis of primary gastric cancer, lymph nodes, and distant metastases. Moreover, in a relatively new single-center retrospective study [8], the novel tracer Ga-FAP (a gallium-68 labeled fibroblast activation protein inhibitor) showed 97.4% sensitivity for lymph node metastasis in PET/CT, compared with 42% for conventional FDG-PET. The detection rate of distant metastasis was 97.2% (compared with 43.1% for conventional FDG-PET). This indicates that PET/CT has significant potential value in the preoperative staging of gastric cancer, especially in the detection of lymph node metastasis.

2.5. Diagnostic Laparoscopy

In modern times, laparoscopic technology has also been developed in the field of gastric cancer therapy. Simultaneously, laparoscopic diagnostic exploration has become one of the preoperative staging methods for gastric cancer because of the advantages of less trauma and rapid recovery. With the implementation of this examination scheme, information such as the location and size of the tumor in the abdominal cavity and the surrounding tissues and organs can be collected. A 2022 study highlighted that even [9] if CT examination is normal. Laparoscopy remains capable of identifying occult peritoneal metastases in ap-

proximately 15% - 20% of cases, thereby directly informing clinical management strategies.

3. The Exploration of Neoadjuvant Therapy Options

3.1. The Status and Common Regimens of Neoadjuvant Chemotherapy for Gastric Cancer

Neoadjuvant therapy is a standard part of the treatment of gastric cancer, which mainly includes chemotherapy, radiotherapy, targeted therapy, and immunotherapy. Its basic principle is to downstage the tumor to promote resection and eradicate micrometastatic tumor cells before and after surgery. For patients with advanced gastric cancer, the core approach of neoadjuvant therapy involves chemotherapy, which enhances prognosis by facilitating tumor downstaging and improving survival rates [10]. At present, there is no unified chemotherapy regimen, which is mainly based on combination drugs. At present, the mainstream neoadjuvant chemotherapy regimens in China mainly include FLOT (fluorouracil, calcium folinate, oxaliplatin plus docetaxel) regimen, FOLFOX (oxaliplatin, leucovorin plus fluorouracil) regimen, SOX (oxaliplatin plus S-1) regimen, and XELOX (oxaliplatin plus capecitabine) regimen [11]. On this basis, various targeted drugs and immunotherapies are combined to form a neoadjuvant plan.

3.2. ECF Therapy in the Perioperative Period

Following the MAGIC trial, perioperative chemotherapy has emerged as a standard strategy for managing gastric cancer. In this study, subjects with operable adenocarcinomas involving the stomach, gastroesophageal junction, or distal esophagus were allocated to either combined modality therapy—comprising three cycles of epirubicin, cisplatin, and fluorouracil both preoperatively and postoperatively—or surgical intervention alone. The results showed significantly improved overall survival (OS) with perioperative neoadjuvant chemotherapy (including 5-year OS, 36.3% vs. 23%) [12]. The results of the MAGIC trial have shown great value and significance in the comprehensive therapy of gastric cancer, perioperative chemotherapy demonstrated a significant survival benefit in resectable gastric cancer patients, elevating the 5-year overall survival rate from 23% to 36% (absolute increase of 13%) compared to surgery alone. This improvement corresponds to a 25% reduction in the risk of death (HR 0.75; 95% CI 0.60 - 0.93). Subsequently, the therapy regimen of oral capecitabine instead of continuous intravenous infusion of 5-FU, namely ECX regimen (epirubicin, cisplatin and capecitabine), effectively improved patient compliance and significantly reduced the incidence of deep vein catheter-related infection and other complications compared with the ECF regimen [13]. Although the MAGIC trial represents an important milestone, much needs to be done. Merely 49.5% of the cohort finalized the intended six-cycle chemotherapy course (comprising three preoperative and three postoperative cycles), while postoperative adjuvant therapy was not administered to a majority exceeding 50% of patients.

3.3. The Application of FLOT in Neoadjuvant Therapy for Gastric Cancer

Over time, a German academic study compared FLOT with ECF/ECX, and the phase II study showed that FLOT was associated with higher R0 resection rates (85% vs. 74%, P = 0.02) and tumor reduction rates (≤ypT2, 44% vs. 27%, P = 0.01). But there were also higher [14] rates of neutropenia, diarrhea, and neurotoxic effects. Subsequently, the FLOT-AIO trial [15], published in the Lancet in 2019, assessed an evidence-based perioperative chemotherapy strategy for resectable gastric adenocarcinoma. Patients with resectable gastric or gastroesophageal junction adenocarcinoma (cT2 or higher and/or cN + resectable tumors, without evidence of distant metastasis) were randomized to receive ECF/ECX chemotherapy, surgery, or four pre- and post-operative cycles of FLOT chemotherapy. Patients receiving FLOT exhibited a median survival duration of 50 months, notably exceeding the 35 months observed with ECF/ECX regimens. Similarly, the 3-year survival rate for FLOT-treated individuals reached 57%, compared to 48% in the ECF/ECX cohort, and complete pathological resolution was 16% and 6% in the FLOT and ECF/ECX groups, respectively. At present, FLOT protocol is designated as a Class I preferred perioperative chemotherapy for locally advanced gastric or gastroesophageal junction adenocarcinoma in current clinical guidelines, including those issued by the National Comprehensive Cancer Network and the European Society of Medical Oncology guidelines (NCCN, ESMO) [16] [17]. A study from Italy showed that patients with high expression of MSI-H (microsatellite instability high) showed a trend of better disease-free survival (DFS) compared with the microsatellite stable (MSS) group in the perioperative therapy with FLOT regimen [18]. On this basis, Floriana [19] *et al.* also pointed out that after the perioperative application of FLOT regimen, the progression-free survival/overall survival (PFS/OS) of the MSI-H group was significantly longer than that of the MSS group, and MSI-H was an independent positive prognostic factor. MSI-H gastric cancer patients may break through the limitations of 5-FU resistance and benefit from the FLOT regimen. The use of pembrolizumab for MSI-H solid tumors has been an important breakthrough in clinical therapy. The KEYNOTE-585 [20] trial evaluated the efficacy of neoadjuvant/adjuvant pembrolizumab combined with chemotherapy (including a subgroup of FLOT regimens) in locally advanced resectable GC/GEJC, and the effect of neoadjuvant/adjuvant pembrolizumab combined with chemotherapy (including a subgroup of FLOT regimens) in locally advanced resectable GC/GEJC was evaluated. The pathological complete response (pCR) rate in the combination group was 10.9% higher than that in the placebo group (P < 0.001), but there was no significant survival benefit. In this direction, we still need to wait for the final data of the study and optimize the biomarker screening strategy.

3.4. FOLFOX Therapy in the Perioperative Period

In 2012, a prospective non-randomized controlled trial of neoadjuvant chemo-

therapy was conducted in China, and the results showed that patients treated with the FOLFOX regimen during the perioperative period and the FOLFOX regimen after surgery had a higher 4-year survival rate (78% vs. 51%, P = 0.031) and disease-free survival rate (78% vs. 48%, P = 0.031). Conclusions: FOLFOX is effective in the therapy of colorectal cancer. The trial also said that the most common side effect of the regimen was grade 1 - 2 leukopenia, and no grade 3 neuropathy, grade 4 cytopenia, or therapy-related deaths [21] were noted. Although the FOLFOX regimen has achieved certain results in past gastric cancer studies, in some clinical trials, compared with other chemotherapy regimens, the FOLFOX regimen is inferior to the FLOT regimen in terms of objective response rate, pathological complete response, tumor marker inhibition, PFS, and OS. It only has certain advantages in terms of neurotoxicity and hair loss risk. Further research is still needed for the simple FOLFOX regimen [22] [23]. Wang Xiang [24] *et al.* published a trial study on the application of the modified FOLFOX6 (mFOLFOX6) regimen in the perioperative period in patients with locally advanced gastric cancer. Among the 73 patients included in the study, the rate of radical surgery was as high as 91.8%, and 45.8% of the patients achieved partial remission. A total of 49.2% of the patients had a tumor growth inhibition rate (GHR) ≥ 50%. Simultaneously, merely a minority cohort (21.8%) exhibited severe (grade 3 - 4) toxic effects, with chemotherapy causing neither mortality nor major complications. mFOLFOX6 can be used as a safe, effective, and well-tolerated neoadjuvant chemotherapy option for patients with locally advanced gastric cancer. In addition, a chemotherapy-only study [25] of bermatuzumab (a humanized monoclonal antibody against fibroblast growth factor receptor 2b [FGFR2b]) plus mFOLFOX6 was performed as first-line therapy, and the combination was used to treat patients with advanced gastric cancer. In East Asian patients with advanced GC/GEJC and FGFR2b overexpression, relative to the placebo plus mFOLFOX6 cohort, the combined therapeutic strategy demonstrated a marked clinical advantage. Specifically, PFS was extended to a median of 12.9 months versus 8.2 months in the control group, while OS reached 24.7 months compared to 12.9 months with placebo, indicating superior efficacy for the combination therapy. Although the mFOLFOX6 regimen has achieved some clinical results in combination with new targeted drugs, the mechanism verification at the gene level is still not perfect.

3.5. The Potential Role of XELOX in Gastric Cancer

The CLASSIC study [26] showed that, compared with surgery alone, XELOX chemotherapy significantly improved the survival rate of patients with advanced gastric cancer after D2 gastrectomy (the 5-year disease-free survival rates were 67% and 53%, respectively, P < 0.0001), and the risk of death was reduced by 34% (P = 0.0015). The adjuvant chemotherapy regimen for gastric cancer has been further expanded. To date, the guidelines for the diagnosis and treatment of gastric cancer formulated by ESMO [27] for gastric cancer patients in different regions

of Asia recommend the application of adjuvant chemotherapy (such as the XELOX regimen) combined with radical surgery as one of the standard therapy options for patients with advanced gastric cancer. In a study [28], the 5-year survival rate of patients with stage III gastric cancer who received XELOX chemotherapy after surgery was significantly higher than that of those who received FOLFOX chemotherapy (65.83% vs.74%, P = 0.002), and the recurrence rate was also lower (69.19% of patients survived for more than 5 years). The XELOX regimen has a clear survival advantage over the FOLFOX regimen. But in a retrospective study, YING Chenhui [29] selected 40 patients with advanced gastric cancer as the study group, who were treated with the XELOX regimen before laparoscopic radical gastrectomy. Compared with 40 patients in the control group who were treated with laparoscopic radical gastrectomy alone, the combination of XELOX neoadjuvant chemotherapy with laparoscopic surgery significantly enhanced clinical outcomes. Key improvements include reduced operative duration, shorter hospitalization, decreased intraoperative bleeding, lower postoperative serum tumor biomarker concentrations, diminished relapse risk, and higher 1-year postoperative survival rates. Additionally, XELOX adjuvant therapy demonstrated a 14% absolute improvement in 5-year survival over surgery alone (58.2% vs. 44.2%, P = 0.025) for advanced gastric cancer patients following D2 gastrectomy, outperforming FOLFOX regimens in survival benefit, but did not improve the overall 5-year survival rate compared with FOLFOX6 (48.5% vs. 42.7%, P = 0.685). Compared with the FOLFOX6 regimen, the XELOX regimen did not improve the overall 5-year survival [30]. Recently, a study of sintilimab combined with XELOX as neoadjuvant therapy showed that the pCR rate of this regimen after surgery was 33.3%, which was significantly higher than the 4.0% - 6.3% of the XELOX regimen and 16.0% of the FLOT-4 trial, and the tumor major pathological response (MPR) rate was 63.3%. These results suggest that this combination regimen may enhance [31] antitumor activity. Nowadays, immunotherapy combined with chemotherapy has become the first-line therapy for advanced [11] metastatic gastric cancer recommended by Chinese guidelines.

3.6. The Evolving Role of SOX in the Therapy of Gastric Cancer

In 2021, the RESOLVE [32] study report suggested that perioperative application of the SOX regimen (3 cycles before surgery and 5 cycles after surgery) had a longer DFS than perioperative application of the XELOX regimen, and the R0 resection rate of SOX perioperative application was as high as 93%. Although this study confirmed the superiority of SOX neoadjuvant chemotherapy, there are still some limitations. For example, the difference between neoadjuvant and adjuvant therapy under the same chemotherapy regimen has not been directly compared, and the long-term survival data are insufficient. In a retrospective analysis, Wang [33] *et al.* classified patients into intestinal and non-intestinal gastric cancers according to Lauren's classification. Based on the chemotherapy protocols administered, participants were categorized into SOX and XELOX cohorts. Analysis re-

vealed that among non-intestinal subtype patients, the SOX cohort exhibited superior 3-year disease-free survival (72.5% vs. 54.5%) and 5-year overall survival (66.8% vs. 51.8%) compared to the XELOX cohort, with both comparisons reaching statistical significance (P = 0.037 and P = 0.038, respectively). SOX regimen for XELOX regimen in patients with non-intestinal gastric cancer may help patients reap more survival benefits. In recent years, a study using the neoadjuvant PD-1 inhibitor tislelizumab combined with the SOX chemotherapy regimen showed [34] that 32 patients had a tumor MPR rate of 53.1%, a pCR rate of 25.0%, and a one-year OS of 91.4% after completing three cycles of neoadjuvant therapy. In addition, 24 patients (65.6%) experienced adverse events, of which four patients (12.5%) experienced grade III-IV adverse events during neoadjuvant therapy. The SOX regimen plays an important role in the exploration of the combined application of chemotherapy and immunotherapy.

4. Surgery Combined with Neoadjuvant Therapy

Advances in the Integration of Surgical Treatment and Perioperative Chemotherapy

Surgical resection is the primary therapy for locally advanced gastric cancer. Complete resection can remove the tumor that is visible within the surgical field. In addition to gastrectomy, lymph node dissection is mandatory, as pathological lymph node metastases are reported in 15% of pathologic T1a or T1b tumors, 40% of T2 tumors, 50% to 60% of T3 tumors, and 70% of T4a tumors [35]. However, there is no clinical method to detect micrometastatic tumor cells in lymph nodes. Since 1990, several phase III trials have evaluated dissection of both the first and second perigastric nodes (D2) in patients with resectable gastric cancer. One trial [36], conducted in the Netherlands, did not show a survival advantage for D2 versus dissection of the first perigastric node (D1) alone. However, the collected follow-up data clearly show that gastric cancer-related mortality is significantly lower after D2 resection than after D1 resection. Given these findings, D2 radical gastrectomy is established as the standard surgical approach for locally advanced gastric cancer in East Asia [37]. As research on gastric cancer progresses, investigations into combining D2 radical resection with neoadjuvant chemotherapy are emerging. A prospective non-inferiority randomized controlled trial conducted in China has initiated exploration in this field, patients were divided into two groups: laparoscopic-assisted distal gastrectomy (LADG) with D2 lymphadenectomy or open distal gastrectomy (ODG) with D2 lymphadenectomy. Patients in the group received three cycles of XELOX before surgery and five cycles of XELOX after surgery. The results showed that the incidence of postoperative complications in the LADG group was significantly lower than that in the ODG group, the incidence of postoperative complications was significantly lower (20% vs. 46%), the pain analogue scale score was lower, and the completion of neoadjuvant chemotherapy was better. Compared with ODG, LADG may provide better postoperative safety and toler [38] ability for neoadjuvant chemotherapy. Therefore, lapa-

roscopic gastrectomy is safe for patients receiving neoadjuvant chemotherapy regimens.

5. Precision Treatment of Gastric Cancer in the Future

The Role of Biomarkers in Neoadjuvant Therapy

In the realm of neoadjuvant chemotherapy (NAC) for gastric cancer, key predictive biomarkers play a pivotal role in individualized treatment. In traditional chemotherapy regimens, metabolic enzymes such as thymidylate synthase (TS), dihydropyrimidine dehydrogenase, and glutathione S-transferase are associated with the sensitivity to fluorouracil-based drugs. Among them, low expression of TS may suggest increased sensitivity to chemotherapy [39]. Inflammatory markers, including the neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein, are also correlated with the efficacy of NAC. Patients with a high NLR exhibit augmented resistance to the S-1 combined with cisplatin regimen. In a study of advanced gastric cancer patients, it was observed that the median OS of the patient group with NLR > 3.0 was significantly shorter than that of the group with NLR ≤ 3.0 ($P < 0.0001$). This directly indicates that a high NLR portends poor outcomes following chemotherapy [40]. MSI-H status in gastric cancer pathological immunohistochemistry is not only associated with immunotherapy but may also enhance sensitivity to platinum-based chemotherapy [41]. In the context of immunotherapy, MSI-H/mismatch repair deficiency (dMMR) serves as the most potent predictive biomarker. The high tumor mutation burden and immune infiltration characteristics of tumors make patients highly sensitive to PD-1 inhibitors [42]. For example, in the NEONIPIGA trial, for GC/GEJC patients with dMMR/MSI-H expression, the pathological complete response rate of neoadjuvant immunotherapy alone (without chemotherapy) reached 58.6% [43]. Gastric cancer patients with Epstein-Barr virus (EBV) positivity demonstrate a better response to immunotherapy due to high PD-L1 expression and lymphocyte infiltration [44]. In targeted therapy, HER2 overexpression remains the core biomarker [45], guiding the application of trastuzumab in combination with chemotherapy. Regarding emerging biomarkers, Claudin 18.2 shows promise in specific subtypes. The SPOTLIGHT trial [46] evaluated the efficacy of first-line zolbetuximab combined with mFOLFOX6 against placebo combined with mFOLFOX6 in patients with claudin 18.2 positivity, HER2 negativity, and locally advanced unresectable or metastatic GC/GEJC. Compared with the placebo group, zolbetuximab combined with mFOLFOX6 significantly prolonged PFS and OS. Specifically, the median PFS of the zolbetuximab group was 10.61 months, while that of the placebo group was 8.67 months (HR 0.751, $P = 0.0066$). The median OS of the zolbetuximab group was 18.23 months, while that of the placebo group was 15.54 months (HR 0.75; 95% CI 0.60 - 0.94, $P = 0.0053$). The GLOW study [47], conducted concurrently with this trial, also arrived at similar conclusions. Although this trial has yielded encouraging results, more clinical trials are required for further validation.

6. Conclusion

Early detection of gastric carcinoma is critical for optimizing clinical outcomes. Developing novel diagnostic approaches enhances tumor detection precision, facilitates accurate clinical staging, and informs clinical decisions regarding neoadjuvant chemotherapy utilization. Furthermore, NAC constitutes an established therapeutic component for gastric cancer management, significantly enhancing survival outcomes. NAC administration reduces primary lesion dimensions, eradicates microscopic metastatic foci, lowers pathological staging, and elevates R0 resection rates—constituting distinct therapeutic benefits of this preoperative strategy. However, the preferred therapy differs by regions [48] [49]. The choice of surgical approach can lead to differences in staging accuracy, which in turn affects the selection of chemotherapy regimens. D2 lymph node dissection can detect more lymph nodes and improve the accuracy of pathological staging, while insufficient dissection may underestimate the stage. In the early MAGIC trial in European countries, only 10% of patients received D2 lymph node dissection, with the majority undergoing D0/D1 lymph node dissection. Based on this trial, European countries more recommend the preoperative and postoperative application of ECF or FLOT regimens. The FLOT regimen has gradually taken the leading position in recent years due to its stronger efficacy. However, the standard protocol recommended by CSCO is D2 radical surgery plus postoperative adjuvant chemotherapy, and XELOX or SOX regimens are recommended for 6 to 8 months postoperatively. Overall, D2 radical surgery combined with neoadjuvant chemotherapy is now the globally recognized standard for gastric cancer treatment. It is suggested to conduct standardized global research to further explore the survival benefits of more intensified neoadjuvant chemotherapy regimens combined with D2 radical surgery. On the other hand, the addition of emerging molecular targeted drugs is expected to further improve the survival of patients, but related studies are still needed to determine the specific molecular markers. Neoadjuvant chemotherapy combined with immunotherapy has also become an important exploration direction in the field of tumor therapy in recent years. At present, more clinical trials and molecular verification are still needed to provide safer and more effective therapeutic options for the majority of gastric cancer patients.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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