Research Progress on Transformation Therapy for Unresectable Gastric Cancer

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Abstract: Gastric cancer is one of the malignant tumors with the highest incidence rate in the country, and ranks the third in cancer related deaths. At present, surgery is still the main means of curative treatment for gastric cancer, but 30% to 40% of patients with advanced gastric cancer lose the opportunity for curative surgery at the initial diagnosis. Therefore, transforming unresectable gastric cancer into resectable gastric cancer is the best choice for patients to achieve "cure". With the emergence of new drugs, the diversification of treatment methods, and the development of multidisciplinary diagnosis and treatment models in recent years, the concept of "translational therapy" has emerged, thereby extending the survival time of patients and improving their quality of life. This article provides a review of the current status and progress in the treatment of unresectable gastric cancer, as well as the application of transformation therapy.

Keywords: unresectable gastric cancer; transformation therapy; surgical procedures; chemotherapy

Gastric cancer (GC) is one of the malignant tumors with the highest incidence rate in China. The long-term survival rate of patients with advanced gastric cancer is low, ranking third in cancer related deaths [1]; China is a high-risk area for gastric cancer. Palliative chemotherapy is the main treatment for advanced gastric cancer patients, but many scholars have reported that after receiving systemic chemotherapy, some patients may experience tumor remission, deterioration, and even have the opportunity for "curative gastric cancer surgery", which prolongs the overall survival time [2]. Therefore, experts from various countries have proposed "transformation therapy" strategies for unresectable gastric cancer. However, it is worth further exploring that the research results are not consistent across different periods and regions, and there are many controversies regarding the chemotherapy regimen, surgical timing, postoperative complications, and conversion rate of transformation therapy for gastric cancer. This has also made transformation therapy a hot and difficult topic in various research centers. In order to further explore related issues such as "transformation therapy", this article reviews the current status and progress of the treatment of unresectable gastric cancer, as well as the clinical application of transformation therapy.

1 The concept and treatment status of unresectable gastric cancer

Non resectable gastric cancer refers to advanced gastric cancer that is difficult to perform R0 resection of the tumor through surgical treatment at the initial diagnosis, and there may be residual tumor after surgery. This mainly includes the following situations: (1) distant metastasis of unresectable gastric cancer, which refers to the occurrence of distant organ metastasis or intraperitoneal implantation metastasis, including positive free tumor cells in ascites examination; (2) Locally advanced unresectable gastric cancer, including mesenteric root or para aortic lymph node (PAN) metastasis highly suspected by imaging or confirmed by biopsy, as well as lymph node invasion or wrapping around large blood vessels; (3) For certain T4b stage gastric cancer, due to tumor invasion of surrounding organs, extensive adhesions, and tumor fixation, it is either unresectable or difficult to remove, and is also classified as unresectable gastric cancer.

Surgery is the preferred treatment for gastric cancer, and there is a consensus on this. However, due to the poor awareness of health examinations (such as regular gastroscopy) among many patients in China, as well as the unclear clinical symptoms of early gastric cancer patients, the local stage of the tumor is relatively late at the initial diagnosis, and there is already distant metastasis or non resectable lesions found during surgery. Traditional treatment methods for such patients can only provide supportive treatments such as radiotherapy, chemotherapy, targeted therapy, and immunotherapy, and their survival time is often short, The median survival time is only 6 months [3]. For the treatment of unresectable gastric cancer, the current global standard chemotherapy regimen is platinum (cisplatin or oxaliplatin) combined with fluoropyrimidine (5-FU, capecitabine or S-1) [4]. The main treatment methods currently recommended by the US NCCN guidelines, the Japanese gastric cancer protocol, and

the European Oncology Association guidelines are systemic chemotherapy based on fluorouracil and paclitaxel drugs, with a median survival rate much lower than that of advanced gastric cancer patients undergoing radical surgery (17 months) [5]. In some countries and regions, targeted drugs such as trastuzumab and lapatinib are used in combination with chemotherapy to treat advanced gastric cancer, and partial remission or even downgrading of the tumor is found. Mit sui et al. [6] applied the mDCS chemotherapy regimen (docetaxel+cisplatin+S-1) combined with trastuzumab to treat advanced unresectable gastric cancer patients, with a surgical conversion rate of 56.3%, the overall survival time of postoperative patients is greater than 18.3 months. Therefore, it is difficult for patients with unresectable gastric cancer to achieve long-term survival by abandoning surgery and receiving palliative chemotherapy without evaluation and screening.

2 Transformation therapy

In recent years, many clinical research data have shown that some patients with late stage gastric cancer and initially diagnosed as unresectable have the opportunity for radical surgical resection after receiving systemic chemotherapy [7]; There is also evidence to suggest that for the treatment of unresectable gastric cancer, combination chemotherapy is more effective than monotherapy in terms of overall survival for patients [3]. Therefore, in the long-term treatment of unresectable gastric cancer patients, some have proposed a "transformation therapy" strategy for unresectable gastric cancer. "Transformation therapy" is a treatment method that uses radiation, chemotherapy, and other methods, relying on auxiliary examinations such as abdominal CT, endoscopic ultrasound, tumor markers, and laparoscopic exploration to evaluate the patient's condition. It transforms advanced tumors that initially cannot achieve curative effects into treatment methods that can achieve R0 resection. In other words, "transformation therapy" combines the effects of combination chemotherapy and surgical treatment. Firstly, personalized periodic chemotherapy is implemented based on the clinical stage of the patient's tumor, and then the optimal surgical timing and method are determined based on the effectiveness of the chemotherapy regimen. A large number of research results indicate that conversion therapy provides new treatment strategies for patients with advanced gastric cancer, prolonging their survival time, improving their quality of life, and providing comprehensive treatment.

2.1 From the concept of "Transformation Therapy" to clinical application

The first report on conversion surgery was proposed by Nakajima et al. [8] in 1997. In this trial, 30 patients with incurable gastric cancer received combination chemotherapy and radical surgery, respectively. The 5-year survival rate of patients who underwent radical resection was 55.6%. Satoh et al. [9] conducted studies on the use of S-1 plus cisplatin combined with gastrointestinal resection and postoperative S-1 treatment for stage IV gastric cancer. The results showed that out of 44 patients who received preoperative chemotherapy, 26 underwent R0 surgical resection; Moreover, among 12 patients, positive cytology as a single factor for stage IV gastric cancer achieved R0 resection, with a 2-year survival rate of 75%. In a study by Yamaguchi et al. [10], 249 patients with stage IV gastric cancer, of which 84 underwent conversion surgery after chemotherapy, and the median survival increased from 24.7 months to 31.0 months; The median survival of patients undergoing R0 resection was 41 Three months. Morgagni et al. [11] reported that out of 22 patients who were unable to achieve curative resection after induction chemotherapy, 9 patients underwent gastrectomy combined with hyperthermia and intraperitoneal chemotherapy, with 1-year and 3-year survival rates of 63.6% and 39.4%. This also indicates that it is safe and feasible for patients with unresectable advanced gastric cancer initially diagnosed to undergo individualized chemotherapy to stabilize, alleviate, and degrade the tumor, followed by routine laparoscopic gastric cancer surgery.

2.2 The characteristics of unresectable gastric cancer and its application in transformation therapy

Non resectable gastric cancer usually has heterogeneous biological properties and features of distant metastasis, including peritoneal metastasis, hematogenous metastasis, and lymph node metastasis.

2.2.1 peritoneal carcinomatosis

Peritoneal metastasis is the most common mode of metastasis in unresectable gastric cancer. The incidence of peritoneal metastasis in unresectable gastric cancer patients is 14% to 43%, accounting for 35% of all metastasis methods [12]. The prognosis of gastric cancer with peritoneal metastasis is worse than that of other metastatic sites. The peritoneal metastasis of advanced gastric cancer is a dynamic and multi-step process involving several coordinated molecular mechanisms. As reported in a recent review by Kanda et al. [13], peritoneal transmission involves four steps: (1) cells migrate from the tumor site to the abdominal cavity after separation; (2) Tumor adaptation to abdominal microenvironment; (3) Tumor adhesion to mesothelial cells and invasion of cell membranes; (4) Tumor growth and angiogenesis. Nowadays, there are many scoring systems for peritoneal metastasis, which can accurately classify the treatment plan of patients based on the pathway of peritoneal metastasis, and thus grade the prognosis of patients. Okabe et al. [14] pointed out that patients were treated with a chemotherapy regimen (S-1 plus cisplatin) and underwent surgical resection after the disappearance of peritoneal metastasis, resulting in a median survival of 43.2 months; Patients who did not receive chemotherapy underwent surgical resection, with a median survival of only 12.6 months. Overall, the treatment of advanced gastric cancer with peritoneal metastasis is currently an important clinical challenge. Usually, these patients no longer have direct surgical indications, and the overall prognosis is poor. Various treatment guidelines for these patients suggest that conversion therapy should be performed first to gain surgical opportunities and prolong their survival time.

2.2.2 Hematogenous metastasis

Patients with unresectable gastric cancer often have multiple metastatic sites, and hematogenous metastases first metastasize to the liver. Most scholars believe that advanced gastric cancer with liver metastasis usually has poor tissue differentiation, often accompanied by peritoneal metastasis or surrounding tissue infiltration. Therefore, liver metastasis in advanced gastric cancer patients is one of the main causes of death. At present, systemic chemotherapy is the main treatment option for advanced gastric cancer patients who have already experienced liver metastasis, with a median survival time of less than 8 months [15]. Local treatment for liver metastases includes radiofrequency ablation, transcatheter arterial chemoembolization, and hepatic arterial infusion chemotherapy, but the prognosis and survival of patients are poor. Li et al. [16] reported 8 cases of advanced gastric cancer patients with single liver metastasis who received weekly DCF regimen (docetaxel+cisplatin+fluorouracil) chemotherapy before gastric cancer radical surgery. Although there is currently a lack of consensus on the indications for surgery for advanced gastric cancer combined with liver metastasis at home and abroad, the results indicate that surgeons and oncologists should continue to be encouraged to adopt multidisciplinary treatment methods. For gastric cancer patients with a single liver metastasis, it is recommended to prioritize conversion therapy before further evaluating the condition. If the conditions are met, radical surgery should be performed.

2.2.3 Lymph node metastasis

Appropriate lymph node resection has milestone significance in the treatment of gastric cancer. Paraaortic lymph node metastasis or lymph nodes around the liver, spleen, or abdominal artery are often considered unresectable. Some retrospective studies have shown that more than 20% of patients undergoing D2 para aortic lymph node resection have para aortic lymph node metastasis, and the 5-year survival rate of patients with para aortic lymph node metastasis does not exceed 20% [17]. Wang et al. [18] performed transformation therapy on 48 patients with simple para aortic lymph node metastasis of gastric cancer, with an R0 resection rate of 50%. The median survival time of the transformation therapy group and the simple palliative chemotherapy group were 18.1 months and 5.6 months, respectively. Since 2000, trials (JCOG0001, JCOG0405, and JCOG1002) have explored preoperative induction chemotherapy and para aortic lymph node gastrectomy for gastric cancer, as well as their efficacy in treating N2/N3 gastric cancer with larger tumor volumes. According to the JCOG0001 research report, patients who received 2-3 repeated chemotherapy sessions with irinotecan and cisplatin had a lower 3-year survival

rate (27%); On the contrary, the JCOG0405 trial showed a 3-year survival rate of 58.8% in patients who received 2-3 weeks of cisplatin and S-1 treatment before surgery; Similarly, in the JCOG1002 study, 52 patients with advanced gastric cancer received conversion therapy, of which 48 patients underwent surgical treatment and 44 patients underwent R0 resection surgery (84.6%). It can be seen that patients who undergo preoperative induction chemotherapy and para aortic lymph node gastric cancer resection have a significantly increased chance of R0 surgical resection.

3 Transformation therapy issues and prospects

Numerous clinical studies both domestically and internationally have shown that some patients with initial unresectable advanced gastric cancer have the opportunity for radical surgery after transformation therapy, which improves the median survival time of patients. But as is well known, gastric cancer is a malignant tumor with heterogeneous characteristics, and tumor cells can directly spread to the peritoneum through the blood and lymphatic system. In addition, the different methods of cancer cells entering the portal circulation lead to significant changes in the location and tumor volume of metastatic patients. Therefore, few patients with unresectable gastric cancer meet the conditions for conversion surgery. It is worth exploring that there are different opinions on the preoperative chemotherapy cycle and the timing of conversion surgery. For example, if the preoperative chemotherapy time is too short, the conversion treatment effect is not good; If the preoperative chemotherapy time is too long, it is easy to miss the best surgical opportunity. According to domestic research reports, conversion surgery was performed on patients undergoing conversion therapy 4-6 weeks after the end of 4.2 cycles of preoperative chemotherapy [19]. Fujitani et al. [20] studied that patients with advanced gastric cancer received an average of 4.5 cycles of chemotherapy before surgery. Although there is no unified standard for the surgical timing of unresectable gastric cancer and resectable gastric cancer after chemotherapy, it is widely accepted that the recommended surgical timing is when the tumor has the best response to chemotherapy. In addition, multiple incurable factors make it difficult to determine the true prognostic variables and the sensitivity rate of chemotherapy. Research progress in chemotherapy provides significant hope for new drugs, but gastric cancer patients with metastasis have poor compliance and survival rates are still unsatisfactory. In many cases, the boundary between neoadjuvant and translational therapy is still unclear. Therefore, due to this series of heterogeneity, analyzing the efficacy of unresectable gastric cancer transformation surgery is very challenging, and it is also difficult to compare the results of different studies.

With the advancement of medical technology, the combination of targeted chemotherapy and the treatment of advanced gastric cancer, the advancement of new molecular targeted drugs and sensitive molecular biomarkers, can shift the treatment from standardization to individualization, thereby further improving its prognosis. Meanwhile, this treatment model also has the potential to receive increasing attention and research from medical and surgical oncologists. In summary, the transformation treatment of unresectable gastric cancer faces enormous challenges, requiring us to increase clinical and basic research, improve multidisciplinary assistance and other diagnostic and treatment models, so that "transformation treatment" truly benefits advanced gastric cancer patients.

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