

Current status and perspectives of conversion therapy for advanced gastric cancer

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Abstract

The concept and strategy of advanced gastric cancer treatment have gradually undergone profound changes with the in-depth understanding of the biology and heterogeneous characteristics of gastric cancer. Moreover, the development and application of new anticancer drugs, including chemotherapy drugs, molecularly targeted drugs and immunotherapy drugs for advanced gastric cancer are reported. The connotation of conversion therapy refers to the unresectable or borderline resectable tumors for surgical technical and/or oncological reasons, after active and effective chemotherapy and other comprehensive treatment, the primary gastric lesions can be reduced to a lower stage, while the metastatic lesions can be effectively controlled, to achieve R0 resection and improve the long-term survival rate. Current promising research results of conversion therapy are mostly from single-arm phase II clinical studies with small samples or retrospective studies. Conversion therapy still faces many challenges, including limited diagnostic and assessment methods, insufficient evidence of highly effective treatment regimens, difficulty in clarifying surgical indications, etc. Therefore, the integrated conversion therapy for advanced gastric cancer needs to be carried out with the close cooperation of a multidisciplinary team. Prospective, multi-center randomized controlled trial studies should be conducted in the future, and precision medicine such as molecular biology should be combined to provide better anticancer drug regimens and higher-level clinical evidence for conversion therapy of advanced gastric cancer.

Keywords: Gastric cancer; advanced; conversion therapy; multidisciplinary team

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Introduction

The latest epidemiological data show that gastric cancer ranks fifth in incidence and fourth in mortality among malignant tumors worldwide (1). China is the leading country with gastric cancer, accounting for nearly 50% of new cases of gastric cancer globally every year, with an estimated 679,100 new cases and 498,000 deaths every year in China, resulting in a heavy economic and social burden (2). A part of gastric cancer patients in China are in advanced stage at the time of diagnosis, and the mainstay treatment was palliative chemotherapy or best supportive

care with unsatisfactory efficacy, and the median survival time was only about 10 months (3). Surgery does not prolong the survival of patients with advanced gastric cancer and is only considered when acute complications occur, such as hemorrhage, perforation and obstruction (4). Therefore, how to improve the treatment effect of advanced gastric cancer is an urgent problem to be solved.

In recent years, with the in-depth understanding of the occurrence, development and biological behavior characteristics of gastric cancer, as well as the development and application of new anticancer drugs, including chemotherapy drugs, molecularly targeted drugs and

immunotherapy drugs, the treatment concept and strategy of advanced gastric cancer have gradually undergone profound changes. Conversion therapy refers to R0 resection of potentially resectable or unresectable advanced tumors that are initially treated with systemic chemotherapy and whose unresectable factors partially or completely disappear, thus prolonging patients' survival rate and improving their quality of life. However, advanced gastric cancer is a systemic disease with a high degree of tumor heterogeneity, complex and diverse metastasis patterns, wide distribution range and significant individual differences. Therefore, the efficacy of conversion therapy remains to be further verified. Consequently, the current article reviews the definition, treatment strategies, challenges and opportunities of conversion therapy for advanced gastric cancer.

Definition and applicable scope

Nakajima *et al.* (5) first reported the results of conversion therapy for advanced gastric cancer in 1997, and then small sample studies were successively published. Yoshida *et al.* (6) summed up the experience in treating advanced gastric cancer in 2016, and put forward the definition of conversion therapy for advanced gastric cancer. Conversion therapy refers to the unresectable or borderline resectable tumors for surgical technical and/or oncological reasons, after active and effective chemotherapy and other comprehensive treatment, the primary gastric lesions can be reduced to a lower stage, while the metastatic lesions can be effectively controlled, to achieve R0 resection and improve the long-term survival rate.

According to differences in tumor biology and heterogeneous characteristics, Yoshida *et al.* (6) divided advanced gastric cancer into four categories. Category 1: Potentially resectable metastasis, which means macroscopically no peritoneal implantation metastasis and technically resectable metastases, including single liver metastasis, metastasis of para-aortic lymph nodes (No.16a2/b1) or positive cytology (POCY1). Primary tumor resection and metastatic tumor resection should be considered for these patients, irrespective of with or without neoadjuvant chemotherapy. Category 2: Marginally resectable metastasis, which indicates no gross peritoneal implantation metastasis but oncologically or technically unresectable, including two or more liver metastases or metastases >5 cm in diameter, invading the vena cava or portal vein, with other distant metastases such

as lung metastases, metastases of Virchow lymph nodes, or para-aortic lymph nodes (No.16a1/b2). These patients should be considered the primary target of conversion therapy, and R0 resection of the primary lesion and metastatic tumor should be pursued after the complete or partial response (CR or PR) is achieved with chemotherapy. Category 3: Incurable and unresectable metastasis except in certain circumstances of local palliation needs, which refers to patients with macroscopic peritoneal implantation metastasis, and the peritoneal metastasis cannot be radical excised, but palliative treatment is necessary. Such patients have no metastasis to other organs, and the treatment mainly includes systemic chemotherapy or combined intraperitoneal chemotherapy. Volume reduction surgery is still available if the patient can obtain CR, PR or negative cytology (CY0). Category 4: Noncurable metastasis, including macroscopically peritoneal dissemination and organ metastasis regarded as never resectable. In addition to diffused peritoneal metastasis, most of these patients have metastasis to other organs, and tumor resection is difficult for most patients, so palliative chemotherapy or best supportive care should be the mainstay treatment. In conclusion, patients with category 1, 2, and part of 3 gastric cancer are suitable for conversion therapy and are expected to gain survival benefits after surgical treatment. However, gastric cancer patients with category 4 are not suitable for conversion therapy or subsequent surgery, and clinically the focus should be on alleviating symptoms and improving quality of life.

Strategy and efficacy of conversion therapy

The main treatment for advanced gastric cancer is systemic chemotherapy, so choosing a chemotherapy regimen is the key to the success of conversion therapy. The Japanese guidelines for the treatment of gastric cancer are based on results of the Japan Clinical Oncology Group (JCOG) series of clinical trials, namely the START study, ToGA study and AVAGAST study, suggesting SP (S-1 plus cisplatin) as the first-line regimen for patients with negative HER-2, and XP (xeloda plus cisplatin) or DTX (docetaxel plus Xeloda) as the second-line regimen. XP regimen combined with trastuzumab is recommended for patients with positive HER-2 (7-9). Based on the V325 study and the REAL 2 study, the National Comprehensive Cancer Network (NCCN) guidelines in the United States and the European Society for Medical Oncology (ESMO)

guidelines in Europe recommended DCF (docetaxel plus cisplatin plus fluorouracil), ECF (epirubicin plus cisplatin plus fluorouracil) and their three-drug adjustment regimen as first-line chemotherapy for advanced gastric cancer (10,11). The FLOT study in Germany (fluorouracil plus leucovorin plus oxaliplatin plus docetaxel) laid the foundation for a paclitaxel-based three-drug chemotherapy regimen as conversion therapy for advanced gastric cancer (12).

Sym *et al.* (13) reported that the chemotherapy response rate of docetaxel plus capecitabine plus cisplatin regimen in treating unresectable gastric cancer was 65%, the surgical conversion rate was 74%, and the R0 resection rate was 63%. The median survival time after R0 resection was 54.3 months. In a study by Kinoshita *et al.* (14), the chemotherapy response rate of docetaxel plus cisplatin plus S-1 in the treatment of advanced gastric cancer was 73.7%, the surgical conversion rate was 59.6%, and the R0 resection rate was 79.4%. The median survival time of patients with R0 resection was 29.9 months. Mitsui *et al.* (15) found that after docetaxel plus cisplatin plus S-1 regimen combined with trastuzumab in patients with HER2-positive metastatic gastric cancer, the surgical conversion rate was 56.3%, and the overall postoperative survival time was more than 18.3 months. A study by Yamaguchi *et al.* (16) showed 259 patients with stage IV gastric cancer who received docetaxel plus S-1 or SP chemotherapy, of whom 84 patients obtained conversion surgery; among them, the median survival time of patients undergoing R0 surgery was 41.3 months, and that of patients undergoing R1/R2 surgery was 21.2 months.

Individualized strategy for conversion therapy is of great importance for advanced gastric cancer with a high degree of tumor heterogeneity and complex and diverse metastasis, such as more common peritoneal metastasis, liver metastasis and distant lymph node metastasis. For peritoneal metastasis, the PHOENIX study conducted by Ischigami *et al.* (17) showed that for patients with disappeared or significantly improved peritoneal metastasis after neoadjuvant intraperitoneal systemic chemotherapy (NIPS) treatment, radical surgery prolongs survival and improves the quality of life. For liver metastasis, therapies that can enhance resection rate of primary gastric tumors and liver metastases, including systemic chemotherapy, radiofrequency ablation, hepatic artery chemoembolization, portal vein embolization, etc., should be actively tried, and R0 resection is the best choice to prolong survival (18,19). There is no consensus on treating extensive distant lymph

node metastasis. However, for only para-aortic lymph node metastasis, the JCOG0405 trial showed that radical gastrectomy with extended lymph node dissection (D2+ para-aortic lymph node resection) could significantly improve prognosis and prolong survival time after SP regimen conversion therapy (20).

Challenges and opportunities in conversion therapy

Conversion therapy for advanced gastric cancer is a challenging and urgent clinical topic. First, the essence of advanced gastric cancer is a systemic disease with complex and diverse metastasis patterns and wide distribution. Second, advanced gastric cancer is a highly heterogeneous tumor with various biological potential and individual differences. Therefore, conversion therapy for advanced gastric cancer faces many challenges, including limited diagnostic and assessment methods, insufficient evidence of highly effective treatment regimens, difficulty in clarifying surgical indications, etc. Firstly, the clinically commonly used diagnostic methods include computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-CT (PET-CT), ultrasound and endoscopy, etc., which can only determine the location, size, and gross shape of the primary gastric lesion or metastatic lesion. Conventional pathological examination is mainly limited to understanding cancer cell type, degree of differentiation, metastasis, etc. Therefore, it is difficult to individualize the understanding of gastric cancer from the mechanism of tumor occurrence and development, which limits the diagnosis of conversion therapy. Secondly, the conversion therapy of advanced gastric cancer still lacks high-level evidence-based medical evidences, most studies are small-sample, one-armed phase II clinical trials or retrospective studies of relatively small sample sizes, although there are some survival benefits from positive results. Hence, patient selection bias is relatively obvious, the level of evidence is low, and there is still a lack of prospective multi-center randomized controlled trials (RCT) study to verify the clinical benefit. Therefore, most of the current treatment plans refer to the guidelines formulated by NCCN, American Society of Clinical Oncology (ASCO), ESMO, Japanese Gastric Cancer Association (JGCA), etc., and only a few chemotherapy regimens could be selected, making it difficult to achieve “tailored” individualized treatment. Thirdly, REGATTA study confirmed that the previous practice of advocating

palliative tumor resection to reduce tumor load for advanced gastric cancer failed to benefit patients in survival (4). Therefore, systemic chemotherapy should play a “driving role” in advanced gastric cancer conversion therapy, and surgery should play a “supporting” role. However, there are still many unsolved problems in surgery, such as resection criteria, optimal timing for surgery, extent of resection, how to control the injury and prevent postoperative complications, and how to judge the short-term and long-term prognosis. It is extremely difficult to carry out RCT studies in this aspect of clinical practice; therefore, high-level evidence-based medical evidence in the surgical treatment of advanced gastric cancer is extremely scarce at present.

In recent years, with the advent of new anticancer drugs, including chemical synthesis drugs, molecularly targeted drugs and immunotherapy drugs, as well as the improvement of surgical technology, conversion therapy of advanced gastric cancer has gradually become possible, bringing long-term survival opportunities to numerous patients with advanced gastric cancer. In summary, the key points of conversion therapy are to screen the highly selected population (partial unresectable or potentially resectable and relatively localized metastasis), conduct effective chemotherapy, radiotherapy, molecularly targeted therapy and immunotherapy, and try to achieve R0 resection (including primary gastric lesions and metastatic lesions). The focus of conversion therapy is to develop a multidisciplinary team (MDT), which includes department of oncology, surgery, radiotherapy, imaging, pathology, nuclear medicine, endoscopy, nutrition and psychology. The MDT should have regular meeting discussions, closely cooperate and effectively link up, and participate in the whole process of patients' diagnosis and treatment, to benefit patients (21). Taking simultaneous liver metastasis of gastric cancer as an example, the establishment of conversion therapy involves surgical treatment of gastrointestinal surgery and liver surgery, systemic chemotherapy and local interventional therapy, including hepatic arterial infusion chemotherapy, hepatic arterial embolization, local hepatic arterial chemotherapy, as well as radiofrequency ablation and optimal supportive therapy. With the advantage of teamwork, only through MDT discussion can we find the best individualized treatment plan according to the clinicopathological characteristics of patients among various treatments.

It should be pointed out that surgical treatment plays a crucial role in the conversion therapy of advanced gastric

cancer, and is the key to improving the prognosis. Consequently, surgical oncologists play an important role in MDT and conversion therapy. The team of Peking University Cancer Hospital classified advanced gastric cancer into resectable stage IV gastric cancer and unresectable stage IV gastric cancer based on the feasibility of surgical resection (22). The former was divided into low-risk and high-risk groups according to the risk of operation and technical difficulty of resectioning metastases. The low-risk group included single liver metastases, single lobed liver metastases or liver metastasis <3 cm in diameter, tumor invading the colon, pancreatic tail or spleen, P1 peritoneal metastasis, etc. However, the high-risk group had more extensive metastasis than the low-risk group. Direct surgery was not only difficult to obtain R0 resection, but the sacrifices and risks involved in surgery also increased significantly. Unresectable stage IV gastric cancer mainly refers to complicated liver metastasis that is difficult to resect, extensive para-aortic lymph node metastasis, diffused peritoneal metastasis and infiltration of adjacent organs, etc. R0 resection cannot be achieved from the perspective of oncology or surgical technique, so it should be the target of conversion therapy. According to the effect of conversion therapy, unresectable stage IV gastric cancer can be further divided into three groups: 1) Conversion group, which refers to R0 surgical resection after good effect of conversion therapy; 2) Partial conversion group, which refers to the partial success of conversion therapy. Although it is difficult to achieve R0 surgical resection, patients still have certain survival benefits after tumor volume reduction surgery; and 3) No conversion group, the conversion therapy failed to control the tumor effectively, patients did not have operation indications, and the prognosis was poor. This classification based on diagnosis and treatment measures helps select the appropriate patient population for clinical conversion therapy and may be conducive to developing high-level clinical studies.

Conclusion and prospect

With the development and application of new chemotherapeutic drugs, molecularly targeted drugs and immunotherapy drugs, conversion therapy for advanced gastric cancer has gradually become possible, bringing hope for the long-term survival of patients with advanced gastric cancer. Conversion therapy targets at a highly selective population, i.e., patients with potentially resectable or localized metastases, where effective chemotherapy is the

premise and R0 resection is the goal. The whole conversion therapy process should be conducted closely with a multidisciplinary comprehensive treatment team. At present, most of the research results are from single-arm phase II clinical studies with small samples or retrospective studies. In the future, prospective, multi-center RCT studies should be carried out to address the main problems in conversion therapy, and to obtain higher-level clinical evidence. Meanwhile, we should focus on genomics and combine molecular typing and other precision medicine methods to provide a new theoretical basis and treatment strategy for the precision and individualization of conversion therapy for advanced gastric cancer, so as to benefit advanced gastric cancer patients in China and worldwide.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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