



# The necessity of adjuvant radiotherapy for locally advanced gastric cancer in China

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**Abstract:** Nearly 50% of the new gastric cancer cases and gastric cancer-related deaths worldwide occur in China. Although the Guidelines for the Diagnosis and Treatment of Gastric Cancer from the National Health Commission of the People's Republic of China have explicitly emphasized the necessity of adjuvant chemoradiation for gastric cancer, few clinical institutions in China routinely administer postoperative adjuvant radiation therapy in patients with gastric cancer. At present, radical resection combined with postoperative chemotherapy alone is the most common treatment for locally advanced gastric cancer in China. However, several phase III prospective randomized controlled trials in Europe have shown that adjuvant chemotherapy alone after a radical resection does not improve the disease-free survival (DFS) or overall survival (OS) of patients with gastric cancer. As in Japan and South Korea, D2 radical resection is the recommended surgical approach for gastric cancer in China. However, several studies have shown that the rate of D2 resection in the treatment of gastric cancer patients in China is low. Nearly 50% of patients undergo a D0-1 radical resection, even at the leading gastric cancer centers in China. The results of the INT-0116 study in the US suggest that gastric cancer patients who undergo a D0-1 radical resection and have stage T3-4 or N+ disease should receive concurrent postoperative radiation therapy and chemotherapy. In conclusion, many patients with gastric cancer do not receive a standard D2 resection in China. As a result, it is important to consider postoperative adjuvant chemoradiation especially in those patients who undergo a D0-1 radical resection.

**Keywords:** China; gastric cancer; radiotherapy; chemoradiation; D2 lymphadenectomy

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## Introduction

The latest data from the National Cancer Centre shows that the prevalence of gastric cancer is high in China. Chinese patients account for 50% of all gastric cancer cases and gastric cancer-related deaths worldwide. Moreover, the morbidity and mortality caused by gastric cancer

rank second among all types of cancer in China (1). An epidemiologic survey of more than 20,000 patients with gastric cancer found that the 5-year survival rate of gastric cancer in China is only 27.4% (2), while an epidemiologic survey in the US that retrospectively analysed the Surveillance, Epidemiology, and End Results Program

(SEER) database showed that adjuvant radiotherapy is closely associated with the improved survival of patients with gastric cancer (3). Researchers still debate the role of adjuvant radiation therapy for patients with gastric cancer in China. Some Chinese researchers believe that the surgical approach commonly used in the US for gastric cancer does not always achieve a D2 resection, which accounts for only 10% of all surgeries in INT-0116, a pivotal study that demonstrated the effectiveness of postoperative radiotherapy in patients with gastric cancer (4). However, they argue that the D2 resection for gastric cancer is common in China, and as a result, the guidelines used in the US are not applicable to Chinese patients. Literature from reputable resources has shown that the D2 resections are performed in only approximately 50% of cases, even among the best gastric cancer treatment centres in China. It is therefore urgently necessary to discuss the scientific basis and necessity of adjuvant chemoradiation after a radical resection in patients with gastric cancer in China.

### **Limitations of adjuvant chemotherapy alone after a radical resection in patients with gastric cancer**

Adjuvant chemotherapy is now the most common adjuvant therapy for gastric cancer, although the clinical value of adjuvant chemotherapy alone is limited. Although the phase III randomized controlled study, CLASSIC in South Korea, has demonstrated the value of adjuvant chemotherapy for gastric cancer, subgroup analyses in this study showed that some patients did not benefit from adjuvant chemotherapy even after a standard D2 radical resection. The subgroup analysis of CLASSIC showed that capecitabine plus oxaliplatin chemotherapy did not improve the survival of patients with T3-4N0 stage cancer (5).

In contrast, several phase III randomized controlled trials in Europe showed that adjuvant chemotherapy did not improve the overall survival (OS) of patients with gastric cancer. In FFCO 8801 in France, 260 patients with stage II-IV (M0) gastric cancer were randomly assigned to a radical resection plus adjuvant chemotherapy group (5-FU plus cisplatin), or a resection alone group. The 5-year OS rates of these patients were 41.9% and 34.9%, respectively; the 7-year OS rates were 46.6% and 44.6%, respectively. These differences did not reach statistical significance (6). A phase III randomized controlled study sponsored by 23 institutions from the European Organization for the Research and Treatment of Cancer (EORTC) and 16

institutions from the International Cooperative Oncology Group (ICCG) found no significant difference in OS and disease-free survival (DFS) between the adjuvant chemotherapy group and the surgery alone group. This study enrolled a total of 397 gastric cancer patients who were randomly assigned into either an adjuvant chemotherapy group (FAMTX or FEMTX) or a surgery alone group, and found that the 5-year OS rates were 43% and 44% ( $P=0.86$ ), respectively, with 5-year relapse-free survival (RFS) rates of 41% and 42% ( $P=0.87$ ), respectively (7). In addition, GOIM 9602 in Italy showed that adjuvant chemotherapy with the ELFE regimen (epirubicin + 5-FU + leucovorin + etoposide) after a radical resection did not improve the OS or DFS of patients with gastric cancer. This study enrolled 228 gastric cancer patients with stage IB-IIIb disease who underwent a D1 (or above) radical resection and were randomly assigned to receive postoperative chemotherapy (the treatment group) or surgery alone (the control group). The 5-year OS rates were 48% and 43.5% ( $P=0.610$ ), respectively, and the 5-year DFS rates were 44% and 39% ( $P=0.305$ ), respectively (8). GOIRC in Italy also showed that postoperative adjuvant chemotherapy with the PELF regimen (cisplatin + epirubicin + leucovorin + 5-FU) did not improve the OS or DFS (9). These results suggest that adjuvant chemotherapy alone has limitations even after a standard D2 radical resection, and even intensive adjuvant chemotherapy did not improve the survival of patients with gastric cancer who did not undergo a D2 resection. Since most Chinese patients with gastric cancer do not undergo a standard D2 resection, further discussion is needed to determine if adjuvant chemotherapy alone would benefit Chinese patients with gastric cancer.

### **The current state of the surgical treatment of gastric cancer in China**

At present, researchers generally believe that postoperative adjuvant chemotherapy reduces the relapse rate and improves the survival of patients with gastric cancer. Improvements in the surgical approach for gastric cancer resection, especially the wide-spread application of the D2 radical resection, has further reduced the rate of local disease relapse, and improved the OS of patients with gastric cancer. At present, no consensus has been established regarding the value of adjuvant radiotherapy for gastric cancer. In China, the treatment and surgical outcomes of gastric cancer treatment vary a great deal across different regions. It is therefore important to investigate the current state of the surgical

treatment of gastric cancer and discuss the necessity of postoperative adjuvant chemoradiation in China.

Current guidelines in China recommend a D2 radical resection as the preferred way to improve the long-term survival of patients with gastric cancer. However, not all medical institutions have the capacity to perform a standard D2 lymphadenectomy. Studies have shown that even at the leading treatment centres, nearly 50% of advanced gastric cancer patients do not undergo a standard D2 resection in China. Researchers at the Cancer Hospital of Tianjin Medical University retrospectively analysed 1,563 radical resections and found that a D2 radical resection was only performed in 53.2% of cases, and less than 16 lymph nodes were dissected in up to 39.0% of those patients. An additional survival analysis showed that the 5-year OS rate was 35.1% in patients who underwent a D1 resection and 45.5% in patients who underwent a D2 resection ( $P < 0.001$ ). The 5-year OS rate was 36.6% in patients who had less than 16 lymph nodes dissected and 43.1% in patients who had 16 or more lymph nodes dissected ( $P = 0.005$ ) (10). Researchers at the Cancer Hospital of Sun Yat-sen University retrospectively analysed 1,343 cases of gastric cancer that underwent a D2 resection and found that less than 15 lymph nodes were dissected in up to 44.8% of the patients who underwent a “D2 radical resection”. A further survival analysis showed that the 5-year OS rate was 45.9% in those patients who had less than 16 lymph nodes dissected and 68.4% in patients who had 16 or more lymph nodes dissected ( $P < 0.001$ ) (11), suggesting that nearly 50% of the “D2 resections” did not meet the criteria of a D2 resection. Researchers at the First Affiliated Hospital of Sun Yat-sen University retrospectively analysed 1,042 cases of gastric cancer that underwent a D2 radical resection between 1996 and 2007 and found that only 36.9% of those procedures met the criteria of a D2 resection. The 5-year OS rate was 58.0% in patients who underwent a non-standard D2 resection and 68.4% in patients who underwent a standard D2 resection ( $P < 0.001$ ) (12).

These results show that nearly 50% of patients in China do not undergo a standard D2 resection at the leading gastric cancer treatment centres. This rate would be even lower at other centres in China. Radiotherapy is a local therapy that complements surgery. Therefore, it is important to adopt adjuvant chemoradiation to treat gastric cancer in China.

### **The scientific basis for adjuvant chemoradiation in the treatment of gastric cancer**

Studies showed that the risk of local relapse was significantly

higher in gastric cancer patients who did not undergo a D2 radical resection. For these patients, the INT-0116 study in the US showed that adjuvant chemoradiation significantly improved treatment outcomes. Nevertheless, researchers are still debating the role of adjuvant radiotherapy after a D2 radical resection in patients with gastric cancer. In recent years, numerous clinical trials on adjuvant radiotherapy after a radical resection in patients with gastric cancer showed that adjuvant radiotherapy after a D2 radical resection is feasible and safe. In 2005, researchers in South Korea analysed more than 1,000 cases of gastric cancer and found that adjuvant radiotherapy and chemotherapy after a D2 resection further improved the survival of patients with stage II, IIIA, IIIB, and IV disease (13). Researchers at the Samsung Medical Centre in South Korea retrospectively analysed 7,757 cases of gastric cancer that underwent a radical resection and found that concurrent radiotherapy and chemotherapy after a D2 radical resection improved the survival of patients with gastric cancer (14). In 2012, a phase III clinical trial was performed by the National Cancer Centre in South Korea, in which patients were randomly assigned into a chemotherapy or a concurrent radiotherapy and chemotherapy group. The results showed that the DFS and local recurrence-free survival (LRFS) rates were significantly higher in the concurrent radiotherapy and chemotherapy group (15). In addition, a subgroup analysis of the ARITIST study in South Korea showed that of the 396 lymph node-positive patients, the 3-year DFS rate was significantly higher in the concurrent radiotherapy and chemotherapy group (77.5% *vs.* 72.3%,  $P = 0.0365$ ) (16,17). In 2018, researchers in South Korea analysed 1,633 cases of gastric cancer who underwent curative D2 and R0 resection followed by adjuvant chemoradiation or chemotherapy alone and demonstrated pathologically confirmed LN metastasis without distant metastasis. The RFS was significantly higher in the chemoradiation group than the chemotherapy group (18). An on-going phase III clinical trial (ARTIST-II) is investigating postoperative adjuvant chemotherapy alone versus postoperative adjuvant radiotherapy and chemotherapy in lymph node-positive patients after a D2 lymphadenectomy, which may help us understand if adjuvant radiotherapy further improves the survival of lymph node-positive patients. These results show that concurrent adjuvant radiotherapy and chemotherapy after a D2 resection can further improve the survival of patients with gastric cancer and should be widely adopted into clinical practice.

### Combination of adjuvant radiotherapy further reduces the side effects of adjuvant therapy in the treatment of gastric cancer

Several studies on adjuvant therapy for gastric cancer showed that concurrent adjuvant chemotherapy and radiotherapy reduced the number of chemotherapy cycles and the dose of chemotherapy (15-20), thereby reducing the side effects of chemotherapy and increasing the completion rate of adjuvant therapy to 80–90% (13,15-22). The FNCLCC/FFCD (23) and MAGIC (24) studies in Europe and the CLASSIC (5,25) and ACT-GC studies (26) in Asia showed that the completion rates of perioperative chemotherapy and adjuvant chemotherapy were low, only 49.5%, 23%, 67%, and 65.8%, respectively, while the incidence of grade 3 to 4 side effects was high, at 40%, 38%, 56%, and 20.7%, respectively. ARTIST showed that adjuvant radiotherapy reduced the required dose of chemotherapy and the number of chemotherapy cycles, thereby further reducing the side effects of chemotherapy. In this study, 458 gastric cancer patients who underwent a D2 radical resection were randomly assigned to the chemotherapy alone group or the concurrent radiotherapy and chemotherapy group. Radiotherapy reduced the number of intravenous chemotherapy cycles in the concurrent radiotherapy and chemotherapy group by two. Further, the study showed that the treatment completion rate was higher in the concurrent radiotherapy and chemotherapy group than in the chemotherapy alone group [81.7% (188/230) *vs.* 75.4% (172/228)], while the incidence of grade 2 or above hand-foot syndrome was higher in the chemotherapy alone group than in the concurrent radiotherapy and chemotherapy group (17). Chemotherapy and radiotherapy work in different ways in the body and therefore do not produce additive side effects, yielding only reduced chemotherapy side effects.

With recent advancements in radiotherapy technology and equipment, conventional two-dimensional radiotherapy (2D-RT) has been replaced by three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiation therapy (IMRT). Volumetric modulated arc therapy (VMAT) and tomotherapy (TOMO) were developed on the basis of IMRT. Unlike 2D-RT and 3D-CRT, IMRT permits individualized adjustments based on tumour size and the prescribed radiotherapy dose, thus permitting an optimal dose distribution in the target area. This ensures a high irradiation dose in a target area while preventing irradiation of important tissues and organs in the centre or concave part of the tumour, protecting the normal

surrounding tissues, and reducing adverse reactions to radiotherapy. Studies have shown that 3D-CRT permits a good dose distribution and reduces the dose of radiation to the surrounding normal tissues, thus yielding fewer radiotherapy side effects relative to 2D-RT (27). In contrast, IMRT has additional advantages over 3D-CRT and 2D-RT, as it reduces the dose of radiation to the kidneys as well as other normal tissues (28-30).

Researchers in Europe agree that adjuvant radiotherapy may improve the survival of patients with gastric cancer and may even reduce treatment side effects. An ongoing phase III randomized controlled clinical trial, TOPGEAR (31), is investigating whether preoperative radiotherapy plus perioperative chemotherapy may further improve OS, reduce treatment side effects, and improve the quality of life of patients with gastric cancer.

### Precision adjuvant radiotherapy

Researchers are currently focusing on the use of precision radiotherapy with state-of-the-art equipment and technology to screen patient populations who might benefit from radiotherapy. The advent of the linear accelerator, computed tomography (CT) positioning, and three-dimensional radiotherapy (3D-RT) planning systems, as well as the combination of a 3D-RT system and an imaging diagnostic system [CT, magnetic resonance imaging (MRI), positron emission tomography (PET)] permit precise positioning, design, and treatment during radiotherapy, thus minimizing damage to normal tissues and improving cancer treatment. Numerous studies have shown that IMRT and 3D-CRT enable a good dose distribution and reduce the side effects of radiotherapy relative to conventional 2D-RT (27-30).

Recent studies have identified target populations with gastric cancer who benefit more from adjuvant radiotherapy. Macdonald *et al.* showed that patients with intestinal type gastric cancer significantly benefited from adjuvant radiotherapy and chemotherapy (4,32). Kim *et al.* showed that lymph node-positive patients significantly benefited from adjuvant radiotherapy and chemotherapy. ARTIST showed that the positive rate of lymph node involvement (N-ratio) was an independent prognostic factor of DFS. When the N-ratio was greater than 25%, a significant difference was observed in the 5-year DFS rate between the concurrent radiotherapy and chemotherapy group and the chemotherapy alone group (55% *vs.* 28%,  $P=0.020$ ) (33). Therefore, as precision therapy based on molecular classification continues to develop, postoperative

adjuvant radiotherapy is highly recommended in gastric cancer patients with the following high-risk factors: failure to undergo a D2 lymphadenectomy, inadequate lymph node dissection (<15), intestinal gastric cancer, stage T3-4 disease, positive lymph nodes, and a high N-ratio.

## Conclusions

The Guidelines for the Diagnosis and Treatment of Gastric Cancer from the National Health Commission of the People's Republic of China explicitly recommend that "gastric cancer patients who have undergone D0-D1 radical resection with postoperative pathological findings of stage T3, T4, or N+, without distant metastasis, should receive concurrent postoperative radiotherapy and chemotherapy; patients who have undergone standard D2 radical resection with postoperative pathological finding of local lymph node metastasis are recommended to receive concurrent postoperative radiotherapy and chemotherapy." However, at present, postoperative adjuvant radiotherapy is rarely administered to patients with gastric cancer in China. As mentioned above, many patients with gastric cancer do not receive a standard D2 resection in China. As a result, it is scientifically necessary to administer postoperative adjuvant chemotherapy and radiotherapy in patients with locally advanced gastric cancer in China, especially those who undergo a D0-1 radical resection.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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