Factors Influencing Long-term Prognosis in Stage III Gastric Cancer Patients Receiving Adjuvant Chemoradiotherapy after D2 Radical Surgery: A 10-Year Follow-up Study

Authors: Ma Guifen, Zhang Qian, Liu Juan, Sun Jing, Lin Genlai, Sun Jing, Lin Genlai

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Abstract

Background Locally advanced gastric cancer primarily includes stage III gastric cancer, which is mainly managed with comprehensive therapy. Postoperative recurrence is a key factor affecting patient prognosis.

Objective To investigate the factors influencing long-term prognosis in stage III gastric cancer patients undergoing adjuvant chemoradiotherapy after D2 radical gastrectomy.

Methods Patients with gastric cancer who received adjuvant chemoradiotherapy following D2 radical gastrectomy in the Department of Radiation Oncology, Zhongshan Hospital, Fudan University from January 2009 to December 2014 were selected as study subjects. Pathological results were staged according to the 8th edition of the gastric cancer TNM staging system of the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC), with a definitive diagnosis of stage III gastric cancer. All patients were followed up every 3 months in the first postoperative year, every 6 months in the subsequent 2 years, and annually thereafter. The follow-up deadline was December 15, 2021. The Log-rank test was used to compare differences in survival rates, Cox proportional hazards regression analysis was employed to explore factors influencing overall survival (OS) and disease-free survival (DFS), a nomogram was constructed to predict the impact of clinicopathological features on prognosis, and the Kaplan-Meier method was used to compare survival differences among patients with different pTNM stages, ages, lymph node ratios (LNR), and gastrectomy types.

Results A total of 135 stage III gastric cancer patients who underwent postoperative adjuvant radiotherapy were included, with a median follow-up time of

10.48 years. Within 5 years, 70 patients experienced recurrence and 62 died, with 5-year disease-free survival and overall survival rates of 48.1% (65/135) and 54.1% (73/135), respectively. Within 10 years, 74 patients experienced recurrence and 74 died, with both 10-year disease-free survival and overall survival rates at 45.2%. Log-rank test results showed statistically significant differences in 5-year survival rates among patients with different pTNM stages, pT stages, LNR, tumor deposits, tumor locations, and gastrectomy types (P<0.05). Comparisons of 10-year survival rates among patients with different pTNM stages, pT stages, LNR, perineural invasion, and gastrectomy types also revealed statistically significant differences (P<0.05). Multivariate Cox proportional hazards regression analysis revealed that pTNM stage (stage IIIA, OS: HR=0.40, 95%CI=0.19-0.83; DFS: HR=0.40, 95%CI=0.19-0.92), LNR (>50%, OS: HR=1.74, 95%CI=1.03-2.94; DFS: HR=1.87, 95%CI=1.73-1.02), and gastrectomy type (total gastrectomy, OS: HR=2.07, 95%CI=1.22-3.50; DFS: HR=2.02, 95%CI=1.20-3.41) were independent influencing factors for both OS and DFS in stage III gastric cancer patients receiving adjuvant chemoradiotherapy after D2 radical gastrectomy (P<0.05). Additionally, age ($ $40 years, HR=2.19, 95%CI=1.06-4.53) was an independent influencing factor for OS in these patients (P<0.05). Furthermore, the nomogram demonstrated that age, pTNM stage, LNR, and gastrectomy type have predictive value for prognosis in stage III gastric cancer patients receiving adjuvant chemoradiotherapy after D2 radical gastrectomy. Recurrence patterns in postoperative gastric cancer patients: 10 cases (7.4%) had local recurrence (anastomotic and lymph node recurrence within the radiation field), 35 cases (25.9%) experienced peritoneal and pelvic dissemination and implantation, and 37 cases (27.4%) developed distant metastasis (including lung, liver, bone, brain, and other organs); some patients exhibited more than two types of recurrence. Comparisons of postoperative survival curves among stage III gastric cancer patients with different pTNM stages, ages, LNR, and gastrectomy types showed statistically significant differences (P<0.05).

Conclusion The majority of recurrences or deaths in stage III gastric cancer patients receiving adjuvant chemoradiotherapy after D2 radical gastrectomy occurred within 5 years. pTNM stage, LNR, and gastrectomy type are the main prognostic factors for these patients.

Full Text

Risk Factors for Long-Term Prognosis in Stage III Gastric Cancer Patients After D2 Radical Surgery and Adjuvant Chemoradiotherapy: A 10-Year Follow-Up Study

MA Guifen[1,2,3], ZHANG Qian[1,2], LIU Juan[1,2], SUN Jing[1,2,3], *LIN Genlai*[1,2]

[1]Department of Radiation Oncology, Zhongshan Hospital, Fudan University, Shanghai 200032, China

[2]Cancer Prevention and Control Center, Zhongshan Hospital, Fudan University, Shanghai 200032, China
[3]Department of Radiation Oncology, Zhongshan Hospital, Fudan University (Xiamen Branch), Xiamen 361000, China

*Corresponding authors: LIN Genlai, Associate Chief Physician; E-mail: lin.genlai@zs-hospital.sh.cn
SUN Jing, Associate Chief Physician; E-mail: sun.jing@zs-hospital.sh.cn

Abstract

Background: Locally advanced gastric cancer primarily comprises stage III disease, which is managed with multimodal therapy. Postoperative recurrence represents a critical factor affecting patient prognosis.

Objective: To investigate the factors influencing long-term prognosis in stage III gastric cancer patients who underwent D2 radical surgery followed by adjuvant chemoradiotherapy.

Methods: We retrospectively analyzed gastric cancer patients who received adjuvant chemoradiotherapy after D2 radical surgery at the Department of Radiation Oncology, Zhongshan Hospital, Fudan University between January 2009 and December 2014. Pathological staging was performed according to the 8th edition of the TNM staging system by the International Union for Cancer Control (UICC) and American Joint Committee on Cancer (AJCC), confirming stage III disease. All patients were followed up every 3 months during the first year postoperatively, every 6 months during the subsequent 2 years, and annually thereafter. The final follow-up date was December 15, 2021. Survival differences between subgroups were compared using Log-rank tests. Cox proportional hazards regression analysis was employed to identify factors affecting overall survival (OS) and disease-free survival (DFS). A nomogram was constructed to predict the impact of clinicopathological features on prognosis. Kaplan-Meier analysis was used to compare survival differences across various pTNM stages, age groups, lymph node ratios (LNR), and gastrectomy types.

Results: A total of 135 eligible patients were included with a median follow-up duration of 10.48 years. Within 5 years, 70 patients experienced recurrence and 62 died, yielding 5-year DFS and OS rates of 48.1% (65/135) and 54.1% (73/135), respectively. Within 10 years, 74 patients had recurrence and 74 died, with both 10-year DFS and OS rates at 45.2%. Log-rank tests revealed statistically significant differences in 5-year survival rates across different pTNM stages, pT stages, LNR, tumor nodules, tumor location, and gastrectomy types ($P<0.05$). Similarly, 10-year survival rates differed significantly across pTNM stages, pT stages, LNR, perineural invasion, and gastrectomy types ($P<0.05$). Multivariate Cox analysis identified pTNM stage (stage IIIA: OS HR=0.40, 95%CI=0.19–0.83; DFS HR=0.40, 95%CI=0.19–0.92), LNR

(>50%: OS HR=1.74, 95%CI=1.03–2.94; DFS HR=1.87, 95%CI=1.73–1.02), and gastrectomy type (total gastrectomy: OS HR=2.07, 95%CI=1.22–3.50; DFS HR=2.02, 95%CI=1.20–3.41) as independent prognostic factors for both OS and DFS (P<0.05). Age ($ $40 years: HR=2.19, 95%CI=1.06–4.53) was an independent factor for OS (P<0.05). The nomogram demonstrated good predictive accuracy (concordance index=0.69), confirming that age, pTNM stage, LNR, and gastrectomy type predict prognosis. Recurrence patterns included: local recurrence in 10 patients (7.4%, involving anastomotic sites and lymph nodes within the radiation field), peritoneal dissemination in 35 patients (25.9%), and distant metastasis in 37 patients (27.4%, involving lung, liver, bone, brain, and other organs), with some patients experiencing multiple recurrence types. Kaplan-Meier curves showed significant survival differences across pTNM stages, age groups, LNR categories, and gastrectomy types (P<0.05).

Conclusion: Most recurrences and deaths in stage III gastric cancer patients after D2 radical surgery and adjuvant chemoradiotherapy occur within 5 years. pTNM stage, LNR, and gastrectomy type are the primary factors affecting prognosis in this patient population.

Keywords: Stomach neoplasms; D2 resection; Adjuvant chemoradiotherapy; Prognosis; Survival rate; Disease-free survival; Root cause analysis

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Introduction

Gastric cancer remains the fifth most common malignancy globally, with particularly high incidence in East Asia. In 2020, there were an estimated 1.089 million new cases and 769,000 deaths worldwide, making it the third leading cause of cancer-related mortality. In China, gastric cancer ranks as the third most common cancer, with an estimated 509,000 new cases and 400,000 deaths in 2022, and mortality rates in men being twice those in women. The current standard of care for stage III gastric cancer involves comprehensive treatment centered on surgical resection supplemented by chemotherapy and radiotherapy; however, overall prognosis remains unsatisfactory. Postoperative recurrence critically impacts patient outcomes. The early Korean ARTIST trial demonstrated that among patients with stage Ib–IV gastric cancer with lymph node metastasis, those receiving adjuvant chemoradiotherapy had longer disease-free survival (DFS) compared to those receiving adjuvant chemotherapy alone (capecitabine plus cisplatin). Although ARTIST2 included 64%–72% of stage III patients post-D2 surgery, the authors concluded that adding radiotherapy did not provide survival benefit, possibly due to the low metastatic lymph node ratio (LNR) of 0.13 affecting treatment efficacy. Whether radiotherapy benefits certain high-risk subgroups warrants further investigation. High-risk factors for gastric cancer include poorly differentiated histology, extensive lymph node metastasis, lymphovascular and/or perineural invasion, and age under 50 years. Most previous studies have evaluated survival outcomes within 5 years, lacking assessment of

long-term prognosis. Therefore, this study aimed to analyze clinicopathological characteristics and identify risk factors affecting long-term prognosis in stage III gastric cancer patients who underwent D2 radical surgery followed by adjuvant chemoradiotherapy, including TNM stage, LNR, vascular invasion, and perineural invasion.

Methods

1.1 Study Population We retrospectively reviewed gastric cancer patients who received postoperative adjuvant chemoradiotherapy at the Department of Radiation Oncology, Zhongshan Hospital, Fudan University between January 2009 and December 2014. Pathological staging was performed according to the 8th edition of the UICC/AJCC TNM staging system for gastric cancer, confirming stage III disease.

Inclusion criteria: (1) Age 20–75 years who underwent D2 radical surgery; (2) Postoperative pathology confirming stage III gastric cancer without distant metastasis (M0) on clinical or imaging evaluation; (3) Received postoperative adjuvant chemoradiotherapy with informed consent.

Exclusion criteria: (1) Received neoadjuvant therapy; (2) Adjuvant radiotherapy alone without chemotherapy; (3) Positive surgical margins (R1/R2 resection); (4) Insufficient function of major organs (heart, liver, kidney); (5) Concurrent or previous malignancies, or prior radiotherapy/chemotherapy.

This study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (Approval No. B2021-814).

1.2 Treatment Protocols All patients underwent total or subtotal gastrectomy with D2 lymphadenectomy. Lymph node dissection extent followed the Japanese Gastric Cancer Treatment Guidelines (6th edition). Total gastrectomy involved complete gastric removal, while subtotal gastrectomy involved resection of two-thirds of the proximal or distal stomach. Tumor nodules were defined as satellite tumor deposits in perigastric adipose tissue without histological evidence of residual lymph node tissue.

All eligible patients received fluorouracil-based multi-agent chemotherapy postoperatively upon physical recovery, combined with oxaliplatin (85–130 mg/m^2), cisplatin (75–100 mg/m^2), or docetaxel (70–85 mg/m^2). After 3–6 chemotherapy cycles, concurrent chemoradiotherapy was administered. Radiotherapy employed intensity-modulated radiotherapy or three-dimensional conformal radiotherapy (6 MV photon beams). According to NCCN target delineation guidelines, the clinical target volume (CTV) included the anastomosis and regional lymphatic drainage areas (lower esophageal paraesophageal, esophageal hiatus, diaphragmatic, perigastric, celiac trunk, hepatic portal, peripancreatic, or splenic hilar regions, depending on primary tumor location). The planning target volume was defined by adding a 0.5–1.0 cm uniform margin to the CTV. For T4b patients, the tumor bed received 50.0–54.0 Gy. Normal tissue constraints

included: spinal cord maximum dose <45 Gy, lung V20 <15%, small bowel V45 <195 cc, heart V30 <20%, liver mean dose <20 Gy, and bilateral kidney V20 <33%. Concurrent chemotherapy during radiotherapy typically consisted of capecitabine (625–825 mg/m^2) or S-1 (41–60 mg) administered orally twice daily on weekdays for 5 weeks. Adjuvant chemotherapy followed a sequential pattern: 3–6 cycles before radiotherapy, 5 weeks of concurrent chemoradiotherapy, then 0–3 additional cycles within one month post-radiotherapy based on patient performance status.

1.3 Data Collection Baseline data collected included age, sex, pTNM stage, pT stage, pN stage (per AJCC/UICC), LNR, tumor nodules, histological type, vascular invasion, perineural invasion, tumor location, and gastrectomy type. LNR was calculated as (number of metastatic lymph nodes / total lymph nodes examined) × 100%.

1.4 Follow-up Patients were followed every 3 months during the first postoperative year, every 6 months during the subsequent 2 years, and annually thereafter. The final follow-up date was December 15, 2021. Follow-up evaluations included medical history, physical examination, laboratory tests with serum tumor markers (CEA, CA19-9, CA724, CA242), and CT scans of chest, abdomen, and pelvis, plus gastroscopy when indicated. Upon disease recurrence or metastasis after adjuvant therapy, most patients received palliative treatment including radiofrequency ablation, interventional therapy for liver metastases, palliative radiotherapy, chemotherapy, or traditional Chinese medicine. OS was defined as the interval from radical surgery to death from any cause or last follow-up. DFS was defined as the interval from surgery to first progression, recurrence, last follow-up, or disease-related death.

1.5 Statistical Analysis All statistical analyses were performed using IBM SPSS® version 22.0 (Chicago, USA). Log-rank tests compared differences in 5- and 10-year survival rates. Cox proportional hazards regression identified factors influencing OS and DFS, with variables showing $P<0.1$ in univariate analysis entering multivariate analysis to determine independent prognostic factors. A nomogram was constructed based on multivariate analysis results to evaluate predictive value. Kaplan-Meier curves were generated for different pTNM stages, age groups, LNR categories, and gastrectomy types. $P<0.05$ was considered statistically significant.

Results

2.1 Patient Characteristics Among 200 stage III gastric cancer patients who received postoperative adjuvant radiotherapy, 55 were excluded due to incomplete staging data, inappropriate age, or comorbidities, and 10 were lost to follow-up, leaving 135 patients for final analysis. The median follow-up duration was 10.48 years. The cohort comprised 97 men and 38 women, with 39 stage

IIIA, 56 stage IIIB, and 40 stage IIIC patients. Mean age was (54.3$±$10.7) years. Median OS was 5.90 years (range: 0.58–12.60 years), and median DFS was 4.70 years (range: 0.31–12.60 years). The mean radiotherapy dose was 45.0 Gy (range: 45.0–50.0 Gy), with 102 patients (75.5%) completing 4–6 chemotherapy cycles (mean: 5.1 cycles; median: 5 cycles).

Log-rank tests showed no significant differences in 5-year survival rates by age, sex, pN stage, histological type, vascular invasion, or perineural invasion (P>0.05). However, significant differences were observed across pTNM stage, pT stage, LNR, tumor nodules, tumor location, and gastrectomy type (P<0.05). Similarly, 10-year survival rates showed no significant differences by age, sex, pN stage, tumor nodules, histological type, vascular invasion, or tumor location (P>0.05), but differed significantly across pTNM stage, pT stage, LNR, perineural invasion, and gastrectomy type (P<0.05) (Table 1).

2.2 Cox Proportional Hazards Regression Analysis Univariate analysis identified age, pTNM stage, pT stage, LNR, perineural invasion, and gastrectomy type as potential factors influencing OS and DFS (P<0.05). Multivariate analysis confirmed pTNM stage, LNR, and gastrectomy type as independent prognostic factors for both OS and DFS (P<0.05), while age ($ $40 years) was an independent factor for OS (P<0.05) (Tables 2–3).

2.3 Nomogram Model Construction Based on multivariate Cox regression results, a nomogram was developed (Figure 1) with a concordance index of 0.69, indicating good predictive accuracy. The model demonstrated that age, pTNM stage, LNR, and gastrectomy type effectively predict prognosis in this patient population.

2.4 Recurrence Patterns Among 74 patients (54.8%) who experienced recurrence, three patterns were identified: local recurrence in 10 patients (7.4%, involving anastomotic sites and lymph nodes within the radiation field), peritoneal dissemination in 35 patients (25.9%), and distant metastasis in 37 patients (27.4%, involving lung, liver, bone, brain, and other organs). Some patients exhibited multiple recurrence types.

2.5 Survival Analysis by Clinical Factors By December 15, 2021, 70 patients had recurred and 61 died within 5 years, yielding 5-year DFS and OS rates of 48.1% and 54.1%, respectively. Within 10 years, 74 patients had recurred and 74 died, with both 10-year DFS and OS rates at 45.2%. The majority of recurrences and deaths occurred within 5 years. Kaplan-Meier curves demonstrated significant survival differences across pTNM stages, age groups, LNR categories, and gastrectomy types (P<0.05) (Figures 2–5).

Discussion

This long-term follow-up study analyzed clinicopathological characteristics and prognostic risk factors in stage III gastric cancer patients who underwent D2 radical surgery with R0 resection followed by adjuvant chemoradiotherapy. We excluded patients who received neoadjuvant therapy or had positive margins, as these factors influence postoperative staging and prognosis. Stage III gastric cancer patients have worse prognosis and more high-risk factors than stages I–II, representing a substantial proportion of newly diagnosed cases in China. Our 10-year follow-up data showed overall 5-year OS of 54.1% and 10-year OS of 45.2%, with 5-year DFS of 48.1% and 10-year DFS of 45.2%. The vast majority of recurrences and deaths occurred within 5 years.

Another study following 5,235 gastric cancer patients for 5–20 years suggested that stage IIIA requires 7 years of surveillance and stage IV requires 8 years, while optimal follow-up duration for stage IIIB and IIIC remains unclear. Our multivariate Cox analysis demonstrated that postoperative pTNM stage, LNR, and gastrectomy type were independent prognostic factors for both OS and DFS ($P<0.05$), while age was an independent factor for OS ($P<0.05$).

Lymph node metastasis is a crucial prognostic factor. We found that patients with LNR $ $50% had significantly better outcomes than those with LNR >50%, with multivariate analysis confirming LNR >50% as an independent risk factor. The Korean ARTIST2 trial, which included 64%–72% stage III patients post-D2 surgery, found no survival benefit from added radiotherapy, possibly due to low LNR (13%). Our previous study also showed no OS or DFS benefit from adjuvant chemoradiotherapy versus chemotherapy alone in patients with LNR >50% ($P=0.140$). Additionally, a domestic study found that N3 patients did not benefit from adjuvant chemoradiotherapy after D2 gastrectomy. A real-world multicenter retrospective study of 230 D2-resected gastric adenocarcinoma patients showed higher OS with chemoradiotherapy versus chemotherapy alone, but without statistical significance. These findings suggest that patients with extensive lymph node metastasis (LNR >50% or N3) have poorer prognosis with higher distant metastasis risk than local recurrence risk, making local therapy (adjuvant radiotherapy) less impactful. Patients with LNR >50% may require more intensive follow-up, while those with LNR $ $50% may be potential beneficiaries, though excessively low LNR may not yield survival benefits due to inherently better prognosis. The optimal LNR range for maximal benefit requires further investigation.

Total gastrectomy was associated with worse prognosis in stage III gastric cancer patients receiving adjuvant chemoradiotherapy, with 5-year OS of 28.6% versus 60.7% for subtotal gastrectomy. This may relate to tumor location, size, extent of lymph node metastasis, and postoperative quality of life. A meta-analysis showed survival advantages for subtotal over total gastrectomy for distal gastric cancer. For gastroesophageal junction tumors, proximal gastrectomy is indicated when the tumor center is $ $3 cm from the esophagogastric junction,

tumor size $ $7 cm, no macroscopic type IV features, and no serosal invasion; otherwise, total gastrectomy is recommended. Thus, total gastrectomy patients harbor more risk factors contributing to poorer outcomes. A Chinese study of 776 gastric cancer patients undergoing D2 surgery without adjuvant radiotherapy reported local recurrence of 37.3% (including regional lymph node recurrence 19.4%, anastomotic recurrence 6.2%, and tumor bed recurrence 1.4%), distant metastasis 29.0%, and peritoneal metastasis 7.3%; among 346 stage III patients, recurrence was 63.6%. Our 10-year follow-up showed a lower recurrence rate of 54.8% in stage III patients, with local recurrence in 7.4%, peritoneal metastasis in 25.9%, and distant organ metastasis in 27.4%, likely attributable to adjuvant radiotherapy reducing local recurrence. Novel approaches for predicting postoperative recurrence include genomics for peritoneal metastasis and systemic immune-inflammation index (neutrophils × platelets / lymphocytes).

NCCN guidelines suggest younger gastric cancer patients may be more prone to recurrence. Our study confirmed worse prognosis in younger patients, with those $ $40 years showing poorer outcomes than those >60 years. The nomogram also showed younger age contributed higher scores and greater prognostic impact. Genomic sequencing reveals early-onset gastric cancer has distinct mutational features compared to conventional gastric cancer. Subgroup analysis identified age $ $40 years as an independent poor prognostic factor, suggesting younger patients may require more intensive treatment and closer surveillance. However, this retrospective single-arm observational study has limitations including small sample size, incomplete data, and potential selection bias.

In conclusion, most recurrences and deaths in stage III gastric cancer patients after D2 radical surgery and adjuvant chemoradiotherapy occur within 5 years. TNM stage, LNR, and gastrectomy type are key prognostic factors, warranting closer follow-up and individualized treatment strategies for high-risk patients.

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Author Contributions: MA Guifen drafted the manuscript, performed statistical analysis, and revised the paper; ZHANG Qian and LIU Juan were responsible for patient enrollment, follow-up, and data collection; SUN Jing contributed to patient enrollment, analysis, and conceptualization; LIN Genlai designed the study and revised the manuscript, taking responsibility for the overall content.

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ORCID: MA Guifen: https://orcid.org/0000-0001-5523-2886

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Note: Figure translations are in progress. See original paper for figures.