Distinguish the Role of Radiotherapy From Chemoradiotherapy for Gastric Cancer With Behavior of Metastasis-Indolent in Lymph Node

Yunfei Zhi, MMed, Zhousheng Lin, MMed, Jinyuan Ma, MMed, Weiming Mou, MMed, and Xinhua Chen, PhD

Abstract

Background: Although the landmark INT-0116 trial and National Comprehensive Cancer Network (NCCN) guidelines recommended pT3-4Nx gastric cancer (GC) patients to receive chemoradiotherapy, the role of radiotherapy has not been distinguished from chemoradiotherapy. Methods: GC with behavior of metastasis-indolent in lymph node (MILN) being confirmed with more than 15 examined LNs after gastrectomy were identified using the Surveillance, Epidemiology and End Result (SEER) database. The cancer-specific survival (CSS) of subgroups for radiotherapy, chemotherapy, chemoradiotherapy and non-adjuvant-treatment were compared. Propensity score matching (PSM) was performed between radiotherapy and non-radiotherapy subgroups to further distinguish the role of radiotherapy from chemoradiotherapy. Cox regression was performed to identify whether radiotherapy or chemotherapy could independently improve prognosis. Results: We identified 690 MILN GC patients in SEER database. 5-year CSS was 71.9% in radiotherapy subgroup and 75.1% in non-radiotherapy subgroup (HR = 1.013, 95% CI = 0.714-1.438, p = 0.940), 75.6% in chemotherapy subgroup and 68.5% in non-chemotherapy subgroup (HR = 0.616, 95% CI = 0.430-0.884, p = 0.008), 52.5% in radiotherapy-alone subgroup and 71.9% in non-adjuvant treatment group (HR = 1.604, 95% CI = 0.575-4.471, p = 0.360), 72.9% in chemoradiotherapy subgroup and 79.5% in chemotherapy-alone subgroup (HR = 1.365, 95% CI = 0.859-2.172, p = 0.185), respectively. Further, PSM markedly improved balance of variables between radiotherapy subgroup and non-radiotherapy subgroup. After PSM, the role of the variables of radiotherapy and chemotherapy in contributing to improving CSS are consistent with that before PSM. Cox regression showed chemotherapy, tumor size, tumor invasiveness and Lauren classification were independent prognostic factors, but not including radiotherapy. Conclusions: Chemoradiotherapy confers superior prognosis to MILN GC patients compared with surgery alone might only be attributed to chemotherapy rather than radiotherapy.

Keywords
advanced gastric cancer, chemotherapy, radiotherapy, chemoradiotherapy, lymph node

Received: April 23, 2020; Revised: August 11, 2020; Accepted: August 26, 2020.

Introduction

Gastric cancer (GC) is a global health problem, with more than 1 million people newly diagnosed with GC worldwide each year. Currently, surgery remains the cornerstone of treatment for local advanced GC (LAGC), and systematic chemotherapy has been demonstrated that it conferred superior prognosis after gastrectomy. However, the role of radiotherapy was only investigated in combining with chemotherapy, as a part of chemoradiotherapy in Western practices.

Chemoradiotherapy has become the standard treatment and been successfully translated to the community in Western. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines recommended that both pT3-4Nx and pTxN+ GC patients who undergo R0 resection should receive chemoradiotherapy. As early as 2001, the landmark INT-0116 trial in...
the United States established the role of adjuvant chemoradiotherapy in the multidisciplinary approach to the management of LAGC.10,13 Then, the INT0116 trial laid the foundation for the popularity of chemoradiotherapy for curatively resected GC with primaries T3 or greater and/or positive nodes in North America. Additionally, Kozak et al. found that the release of the INT 0116 trial likely reflected the increased use of chemoradiotherapy, which has been associated with improved survival in GC patients, suggesting that the improved outcome seen in this trial has been successfully translated to the community.11 Consistently, some retrospective studies with large sample sizes have also shown the survival advantage of chemoradiotherapy.14-16 However, these studies evaluated chemoradiotherapy versus surgery alone and thus could not distinguish the effect of chemotherapy and radiotherapy from chemoradiotherapy in prolonging survival in Western practices.

On the basis of INT0116 study, the phase 3 Adjuvant Chemoradiotherapy Therapy in Stomach cancer (ARTIST) trial further showed that radiotherapy in addition to capcitabine/cisplatin chemotherapy after radical resection did not improve the 5-year survival rate (73% vs. 75%). Nevertheless, in the subgroup of patients with pathological lymph node (LN) metastasis, who received chemoradiotherapy experienced superior disease-free survival (DFS) to those who received chemotherapy alone. Then, the subsequent trial, ARTIST2, was conducted to investigate whether radiotherapy is beneficial in LN-positive GC. However, the interim analysis of the recent ongoing ARTIST2 study showed that radiotherapy did not provide further benefit in patients with stage II-III lymph node-positive GC after D2 radical resection.17 Thus, currently, radiotherapy is not considered a post-operative adjuvant therapy for GC performed with D2 lymph node dissection in the Western Asia, especially in LN-negative patients. However, the effect of radiotherapy differed between Eastern and Western practices might be attributed to the discrepancy of surgical quality assurance since 54% of patients in the INT0116 trial had D1 lymphadenectomy or less10 while most patients in the INT0116 trial likely reflected the improved use of chemoradiotherapy, which has been associated with improved survival in GC patients, suggesting that the improved outcome seen in this trial has been successfully translated to the community.11 Consistently, some retrospective studies with large sample sizes have also shown the survival advantage of chemoradiotherapy.14-16 However, these studies evaluated chemoradiotherapy versus surgery alone and thus could not distinguish the effect of chemotherapy and radiotherapy from chemoradiotherapy in prolonging survival in Western practices.

Within the SEER database, we identified 44528 patients with GC confirmed by pathological examination and with active follow-up from 2010 to 2016. The cut-off date in this study was 12/31/2016. We excluded patients who met the following criteria: TNM stage without being confirmed by gastrectomy; local LN metastasis (N+) or distant metastasis (M+); and age <18 years old or >85 years old at the time of diagnosis. Depending on the system, 4417 GC patients were identified. Then, to ensure that the patients with N0 status were MILN, the patients with <16 LN examined or primary tumor invasion less than T3 were also excluded. Then, 690 patients were diagnosed with T3/T4, including T3, T4a, T4b, and T4 Nos, N0, and M0 tumors were abstracted and analyzed. The patients who underwent gastrectomy were grouped into the radiotherapy group (n = 288) and non-radiotherapy group (n = 402). To control confounding factors by different indications for radiotherapy between arms, we performed a matched analysis, a total of 218 patients in the radiotherapy group and 218 patients in the non-radiotherapy group were matched at a 1:1 ratio (data extraction flowchart is shown in Figure 1).

The following patients’ information was used in our study: Baseline demographics including sex, age, race, marital status, insurance situation; Tumor features including primary tumor invasion, node status, metastasis status, grade, tumor location, tumor size and Lauren classification; Treatment information including gastrectomy, radiotherapy and chemotherapy. Cancer stage was determined or recoded according to the AJCC/UICC TNM staging system (seventh version).31 Age was categorized into groups of < 60 and ≥ 60 years based on statistical and clinical consideration. Tumor location was categorized as the esophagogastric junction and stomach. Tumor size was recoded as < 5 cm, 5-10 cm, > 10 cm. More details can be obtained from SEERStat software version 8.3.6 and SEER manual 2016.

The endpoint of this study was CSS (Cancer-specific Survival), which was defined as the period from the date of diagnosis to the date of gastric cancer caused death, and patients who survived to the latest follow-up were censored.

Methods

Data Source and Data Selection

This retrospective cohort study assessed the role of radiotherapy in MILN GC (T3-4N0M0) patients whose data were abstracted from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) population-based data registry.20 The SEER database is the most comprehensive cancer registry in the United States and provides information from cancer registries that comprise approximately 28% of the country’s population. SEERStat software version 8.3.6 was published by SEER and was used to identify eligible patients in this study. The software was obtained from the official network (https://seer.cancer.gov/).

Statistical Analysis

Descriptive statistics were used to calculate the absolute number and frequency among patients. The χ², t, or Fisher’s exact
test was used for intergroup comparisons where appropriate. The CSS was computed by the Kaplan-Meier method and tested by log-rank test. Survival-associated factors were evaluated using univariate analysis and multivariable Cox proportional hazards (PH) regression, adjusting for sex, age, race, marital status, insurance situation, primary tumor invasion, Lauren classification, grade, tumor location, tumor size, chemotherapy and gastrectomy.

To control confounding factors by different indications for radiotherapy between arms, we performed a matched analysis. In the case-matched analysis, which aimed to balance high-dimensional observed covariates, propensity score matching (PSM) was applied. The matching factors were the independent prognostic factors found to be unbalanced between the 2 groups confirmed by univariate Cox PH regression. Race, Lauren classification, tumor size and chemotherapy were included. The PH and linearity assumptions for 25 continuous variables were examined using restricted cubic splines. Continuous variables were transformed into adequate forms for fitting the assumptions as appropriate. For categorical variables, log-log survival plots were used to identify the PH assumption, and all variables were fitted to the assumption. Results were considered statistically significant at a 2-sided P < 0.05. Data analysis were performed using IBM SPSS 25.0.0.0 (IBM, Armonk, NY).

**Nomogram Construction and Validation**

Nomogram construction and validation analysis were performed using R 3.4.1. Foreign, Hmisc, survival and rms packages were used. Data were read with the foreign package. Variables were selected using the backward stepwise selection method in the Cox regression model with the survival package. Based on the predictive models with the identified prognostic factors, nomograms were constructed to predict 3- and 5-year CSS. Nomogram validation consisted of discrimination and calibration. Discrimination was evaluated using Harrell’s concordance index (C-index) with the rms package. Nomogram validation consisted of discrimination and calibration. Discrimination was evaluated using Harrell’s concordance index (C-index) with the rms package and Hmisc package. Generally, a higher C-index value indicates better discrimination, with a value of 0.7 indicating moderate discrimination. A time-dependent receiver operating characteristic (ROC) curve was drawn to evaluate the accuracy of the nomogram. Validation was performed by comparing the means of predicted survival with those of actual observed survival estimated by the Kaplan-Meier method. To evaluate the efficacy of the nomogram better, stratification strategy was adopted, the X-tile program (Yale University School of Medicine) was used.
Table 1. Patient and Tumor Characteristics.

| Variable               | Category | Before PSM | After PSM |
|------------------------|----------|------------|-----------|
|                        |          | Radiotherapy [n(%)] | Without Radiotherapy [n(%)] | Statistic | p     | Radiotherapy [n(%)] | Without Radiotherapy [n(%)] | Statistic | p     |
| Year at Diagnosis      | 2010     | 55(19.1)   | 52(12.7)  | 10.927    | 0.053 | 43(19.72%)        | 20(9.17%)     | 14.838   | 0.011  |
|                        | 2011     | 42(14.6)   | 78(19.4)  |           |       | 30(13.76%)        | 41(18.81%)    |          |        |
|                        | 2012     | 41(14.2)   | 67(16.7)  |           |       | 36(16.51%)        | 31(14.22%)    |          |        |
|                        | 2013     | 51(17.7)   | 52(12.9)  |           |       | 38(17.43%)        | 31(14.22%)    |          |        |
|                        | 2014     | 41(14.2)   | 72(17.9)  |           |       | 29(13.30%)        | 42(19.27%)    |          |        |
|                        | 2015     | 58(20.1)   | 81(20.1)  |           |       | 42(19.27%)        | 53(24.31%)    |          |        |
|                        | 2016     | 0          | 0         |           |       | 0                | 0             |          |        |
| Sex                    | Male     | 196(68.0%) | 249(73.2%)| 2.740     | 0.098 | 145(66.51%)       | 137(62.84%)   | 0.643    | 0.423  |
|                        | Female   | 92(31.9%)  | 92(26.9%) |           |       | 73(33.49%)        | 81(37.16%)    |          |        |
| Age                    | <60      | 97(33.6%)  | 103(25.62%)| 4.259    | 0.043 | 96(44.04%)        | 71(32.57%)    | 6.066    | 0.014  |
|                        | ≥60      | 191(66.3%) | 299(74.38%)|           |       | 122(55.96%)       | 147(67.43%)   |          |        |
| Race                   | White    | 218(75.6%) | 254(63.18%)| 12.568   | 0.002 | 153(70.18%)       | 132(60.55%)   | 6.382    | 0.041  |
|                        | Black    | 25(8.68%)  | 60(14.93%) |           |       | 20(9.17%)         | 36(16.51%)    |          |        |
|                        | Others   | 45(15.63%) | 88(21.89%) |           |       | 45(20.64%)        | 50(22.94%)    |          |        |
| Marital status         | Unmarried| 86(28.86%) | 152(37.81%)| 3.920    | 0.141 | 67(30.73%)        | 73(33.49%)    | 0.387    | 0.824  |
|                        | Married  | 189(65.63%)| 229(56.97%)|           |       | 142(65.14%)       | 136(62.39%)   |          |        |
|                        | Unknown  | 13(4.51%)  | 21(5.22%)  |           |       | 9(4.13%)          | 9(4.13%)      |          |        |
| Insurance situation    | Non-insured| 8(2.78%)  | 8(1.99%)  | 1.876    | 0.391 | 5(2.29%)          | 3(1.38%)      | 1.560    | 0.458  |
|                        | Insured  | 273(94.79%)| 273(67.91%)|           |       | 207(94.95%)       | 212(97.25%)   |          |        |
|                        | Unknown  | 7(2.43%)   | 5(1.24%)  |           |       | 6(2.75%)          | 3(1.38%)      |          |        |
| Primary Tumour Invasion| T3       | 229(79.51%)| 313(77.86%)| 0.272    | 0.602 | 171(78.44%)       | 170(77.98%)   | 0.013    | 0.908  |
| Lauren Classification  | Intestinal| 59(20.49%)| 89(22.14%)| 47(21.56%)| 48(22.02) |
|                        | Diffuse  | 39(13.54%) | 86(21.39%)| 36(16.51%)| 37(16.97) |
|                        | Others   | 235(81.60%)| 285(70.90%)| 170(77.98)| 161(73.85) |
| Grade                  | G1-G2    | 108(37.50%)| 128(31.84%)| 84(38.53%)| 59(27.06) |
|                        | G3-G4    | 163(56.60%)| 267(66.42%)| 121(55.50)| 155(71.10) |
|                        | Unknown  | 17(5.90%)  | 7(1.74%)  | 13(5.96)  | 4(2.83)  |
| Tumor Location         | Esophagogastric junction | 142(49.31%)| 81(20.15%)| 0.532    | 0.525 | 120(55.05%)       | 171(78.44%)   | 26.876   | 0.001  |
|                        | Stomach  | 146(50.69%)| 321(79.85%)| 98(44.95%)| 47(21.56) |
| Tumour Size            | <5 cm    | 145(50.35%)| 193(48.01%)| 65.209   | <0.001 | 145(66.51%)       | 112(51.38)    | 11.797   | 0.008  |
|                        | ≥5 cm, <10 cm | 88(30.56%)| 147(36.57%)| 52(23.85%)| 58(26.61) |
|                        | ≥10 cm   | 26(9.03%)  | 32(7.96%)  | 11(5.05)  | 16(7.34) |
|                        | Unknown  | 29(10.07%) | 30(7.46%)  | 10(4.59)  | 22(10.09) |
| Chemotherapy           | No       | 10(3.47%)  | 193(48.01%)| 160.287   | <0.001 | 10(4.59)          | 10(4.59)      | <0.001   | 1.000  |
|                        | Yes      | 278(96.53%)| 209(51.99%)| 208(95.41) | 208(95.41) |
| Gastrectomy            | Distal   | 54(18.75%) | 80(19.90%) | 0.742    | 0.863 | 472(15.60%)       | 412(18.81%)   | 0.471    | 0.925  |
|                        | Total    | 145(50.35%)| 191(47.51%)| 106(48.62) | 111(50.92) |
|                        | Proximal | 12(4.17%)  | 15(3.73%)  | 7(3.21)   | 8(3.67)  |
|                        | Gastrecytomy, Nos | 77(26.74%)| 116(28.86%)| 58(26.61) | 57(26.15) |

Medicine, New Haven, CT, USA) was used to define the optimal cut-off points for the log-rank test and the highest specificity and sensitivity.

Results

Baseline Characteristics and Long-Term Survival

Together, 690 MILN GC patients who underwent gastrectomy between January 2010 and December 2016 were prospectively enrolled. As shown in Table 1, 288(41.7%) patients received radiotherapy and 402(58.3%) patients not; 487(70.6%) patients received chemotherapy and 203(29.4%) patients not; 193(28.0%) patients received no adjuvant treatments, 209(30.3%) patients received chemotherapy alone, 10 patients (1.4%) received radiotherapy alone and 278(40.3%) patients received chemoradiotherapy. Regardless of their assignment in the radiotherapy subgroup or non-radiotherapy subgroup, individuals younger than 60 years of age were more likely to receive radiotherapy than those older than 60 years [48.5% (97/
200) vs. 38.9\% (191/490), \( p = 0.043 \). The tumor size and Lauren classification were unbalanced between the 2 subgroups. The patients who did not receive chemotherapy were generally less likely to receive radiotherapy than those who received treatment with chemotherapy [4.9\% (10/203) vs. 57.08\% (278/487), \( p < 0.001 \)]. No significant differences were found in terms of other variables.

The balance of variables between the subgroups was markedly improved after PSM. Especially, for the variable of chemotherapy, which has been explicit demonstrated to be associated with prognosis in previous trials\(^\text{6-9} \) and our study and be related to the conducting of radiotherapy in our study, the significance of difference (\( p \) value) between radiotherapy subgroup and non-radiotherapy subgroup was changed from 0.001 into >0.500. The baseline characteristics of patients included in this study are listed in Table 1.

After PSM, Kaplan-Meier analysis showed that 5-year CSS was 72.1\% in radiotherapy subgroup and 78.3\% in non-radiotherapy subgroup [HR = 1.259, 95\% CI = 0.788-2.012, \( p = 0.333 \)]; B. 76.4\% in chemotherapy subgroup and 44.0\% in non-chemotherapy subgroup [HR = 0.297, 95\% CI = 0.143-0.621, \( p = 0.001 \)]; C. 52.5\% in radiotherapy alone subgroup and 42.9\% in non-adjuvant treatment subgroup [HR = 0.591, 95\% CI = 0.132-2.647, \( p = 0.487 \)]; D. 73.4\% in chemoradiotherapy subgroup and 79.8\% in chemotherapy alone subgroup [HR = 1.325, 95\% CI = 0.804-2.182, \( p = 0.266 \)].

**Figure 2.** Comparison of cancer-specific survival (CSS) after propensity score matching. A. 5-year CSS was 72.1\% in radiotherapy subgroup and 78.3\% in non-radiotherapy subgroup [HR = 1.259, 95\% CI = 0.788-2.012, \( p = 0.333 \)]; B. 76.4\% in chemotherapy subgroup and 44.0\% in non-chemotherapy subgroup [HR = 0.297, 95\% CI = 0.143-0.621, \( p = 0.001 \)]; C. 52.5\% in radiotherapy alone subgroup and 42.9\% in non-adjuvant treatment subgroup [HR = 0.591, 95\% CI = 0.132-2.647, \( p = 0.487 \)]; D. 73.4\% in chemoradiotherapy subgroup and 79.8\% in chemotherapy alone subgroup [HR = 1.325, 95\% CI = 0.804-2.182, \( p = 0.266 \)].
alone subgroup and 42.9% in non-adjuvant treatment subgroup (HR = 0.591, 95% CI = 0.132-2.647, p = 0.487) (Figure 2C), 73.4% in chemoradiotherapy subgroup and 79.8% in chemotherapy alone subgroup (HR = 1.325, 95% CI = 0.804-2.182, p = 0.266) (Figure 2D). Result of the cohort before PSM were shown in Figure 3, overall, survival outcome between these subgroups was essentially the same before and after PSM.

Univariate and Multivariate Analysis

To explore an optimization model of whether radiotherapy could benefit MILN GC patients, analyses of univariate and multivariate cox regression were conducted in this study (Table 2). Univariate analysis of potential prognostic factors revealed that the patient’s diagnosed year (2010, 2011, 2012, 2013, 2014, 2015), sex, age (<60 vs. ≥60 years old), race (white, black and others), marital status (unmarried, married and unknown), insurance situation, Lauren classification (intestinal, diffuse and unknown), grade (G1-G2, G3-G4 and unknown), tumor location (esophagogastric junction vs. stomach), primary tumor invasion (T3 vs. T4), tumor size (<5 cm, 5-10 cm, ≥10 cm and unknown), chemotherapy (yes or no), radiotherapy (yes or no) and gastrectomy (distal, total, proximal and Gastrectomy, Nos) were regarded as covariates.
Table 2. Univariate and Multivariate Cox Regression Analysis for Cancer-Specific Survival After Psm.

| Variable                  | Univariate Cox regression | Multivariate Cox regression |
|---------------------------|---------------------------|-----------------------------|
|                           | HR | 95% CI    | p   | HR | 95% CI    | p   |
| Year at Diagnosis         |    |           |     |    |           |     |
| 2010                      | 0.941 | 0.47 2.03 | 0.959 | 0.959 |           |     |
| 2011                      | 0.98 | 0.47 2.03 | 0.959 | 0.959 |           |     |
| 2012                      | 0.95 | 0.45 2.01 | 0.900 | 0.900 |           |     |
| 2013                      | 0.98 | 0.45 2.15 | 0.962 | 0.962 |           |     |
| 2014                      | 0.87 | 0.36 2.15 | 0.767 | 0.767 |           |     |
| 2015                      | 1.44 | 0.59 3.56 | 0.425 | 0.425 |           |     |
| Sex                       |    |           |     |    |           |     |
| Male                      | 0.84 | 0.51 1.38 | 0.236 | 0.236 |           |     |
| Female                    | 0.40 | 0.16 0.99 | 0.047 | 0.047 |           |     |
| Age, y                    |    |           |     |    |           |     |
| <60                       | 0.76 | 0.47 1.20 | 0.026 | 0.026 |           |     |
| ≥60                       | 0.90 | 0.55 1.48 | 0.673 | 0.673 |           |     |
| Race                      |    |           |     |    |           |     |
| White                     | 0.50 | 0.27 0.97 | 0.040 | 0.040 |           |     |
| Black                     | 0.40 | 0.16 0.99 | 0.047 | 0.047 |           |     |
| Others                    | 0.27 | 0.08 0.76 | 0.006 | 0.006 |           |     |
| Marital status            |    |           |     |    |           |     |
| Unmarried                 | 0.90 | 0.55 1.48 | 0.673 | 0.673 |           |     |
| Married                   | 0.93 | 0.28 3.08 | 0.903 | 0.903 |           |     |
| Unknown                   | 0.93 | 0.28 3.08 | 0.903 | 0.903 |           |     |
| Insurance situation       |    |           |     |    |           |     |
| Non-insured               | 1.08 | 0.15 7.80 | 0.937 | 0.937 |           |     |
| Insured                   | 1.18 | 0.11 13.05 | 0.891 | 0.891 |           |     |
| Unknown                   | 0.90 | 0.55 1.48 | 0.673 | 0.673 |           |     |
| Lauren Classification     |    |           |     |    |           |     |
| Intestinal                | 0.010 | 0.46 2.80 | 0.028 | 0.028 |           |     |
| Diffuse                   | 6.15 | 1.89 19.97 | 0.003 | 0.003 |           |     |
| Unknown                   | 3.51 | 1.27 9.65 | 0.015 | 0.015 |           |     |
| Grade                     |    |           |     |    |           |     |
| G1-G2                     | 1.34 | 0.79 2.27 | 0.283 | 0.283 |           |     |
| G3-G4                     | 1.96 | 0.67 5.77 | 0.221 | 0.221 |           |     |
| Unknown                   | 1.96 | 0.67 5.77 | 0.221 | 0.221 |           |     |
| Tumor Location            |    |           |     |    |           |     |
| Esophagogastric junction  | 0.92 | 0.57 1.51 | 0.047 | 0.047 |           |     |
| Stomach                   | 0.015 | 0.46 2.80 | 0.028 | 0.028 |           |     |
| Primary Tumor Invasion    |    |           |     |    |           |     |
| T3                        | 1.85 | 1.13 3.03 | 1.69 | 1.69 | 1.01 2.84 | 1.01 2.84 |
| T4                        | 1.08 | 0.63 1.86 | 0.786 | 0.786 | 1.29 0.74 2.26 | 0.367 | 0.367 |
| Tumor Size                |    |           |     |    |           |     |
| <5cm                      | 3.55 | 1.81 6.97 | 0.001 | 0.001 |           |     |
| ≥5cm, <10cm               | 1.06 | 0.38 2.96 | 0.920 | 0.920 |           |     |
| >10cm                     | 1.06 | 0.38 2.96 | 0.920 | 0.920 |           |     |
| Unknown                   | 1.06 | 0.38 2.96 | 0.920 | 0.920 |           |     |
| Radiotherapy              |    |           |     |    |           |     |
| No                        | 1.26 | 0.79 2.01 | 1.24 | 1.24 | 0.77 2.01 | 1.24 | 1.24 |
| Yes                       | 0.30 | 0.14 0.62 | 0.319 | 0.319 | 0.15 0.68 | 0.319 | 0.319 |
| Chemotherapy              |    |           |     |    |           |     |
| No                        | 0.30 | 0.14 0.62 | 0.319 | 0.319 | 0.15 0.68 | 0.319 | 0.319 |
| Yes                       | 0.30 | 0.14 0.62 | 0.319 | 0.319 | 0.15 0.68 | 0.319 | 0.319 |
| Gastrectomy               |    |           |     |    |           |     |
| Distal                    | 1.08 | 0.60 1.95 | 0.791 | 0.791 |           |     |
| Total                     | 0.72 | 0.17 3.11 | 0.655 | 0.655 |           |     |
| Proximal                  | 1.09 | 0.55 2.13 | 0.813 | 0.813 |           |     |
| Gastrectomy, Nos          | 1.09 | 0.55 2.13 | 0.813 | 0.813 |           |     |
Both before and after PSM, the variables with $p < 0.01$ in the univariate survival analysis were further analyzed in multivariate survival analysis, and the variable of radiotherapy was always included in the survival analysis.

The univariate survival analysis revealed that race ($p < 0.05$), primary tumor invasion ($p < 0.05$), tumor size ($p < 0.05$), Lauren classification ($p < 0.05$), chemotherapy ($p < 0.05$), and radiotherapy ($p < 0.05$) were associated with the CSS of the MILN GC patients who underwent gastrectomy, but radiotherapy did not improve survival at all (Table 2).

After PSM, the multivariate survival analysis showed that the patients who had received chemotherapy generally had better CSS (HR = 0.32, 95% CI = 0.15-0.68). Furthermore, patients with T4 tumors were likely to have worse CSS than those with T3 tumors (HR = 1.691, CI = 1.01-2.84). Meanwhile, tumor size also influenced patient prognosis; specifically, patients with bigger tumors (d$\geq$10 cm) had worse CSS (e.g. HR = 2.48, CI = 1.46-4.22). Furthermore, compared with the race of white, black and other ethnic backgrounds were likely to have better CSS (HR = 0.47, CI = 0.18 -1.18 and HR = 0.39, CI = 0.20-0.76, respectively)(Table 2).

Meanwhile, survival analysis was also used to analyze the cohort before PSM, generally, the results were essentially the same, superior CSS remained associated with patients who had received chemotherapy, smaller tumor, less invasive tumors and intestinal-type classification.(Table S1). However, no predominant statistical significance was found for radiotherapy before or after PSM(Table 2& Table S1).

**Prognostic Nomogram Construction and Calibration**

The constructed nomogram (Figure 4) can assign survival probability by adding up the scores identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 3- and 5-year survival.

![Nomograms predicting 3- and 5-year cancer-specific survival (CSS). The nomogram is used by adding up the points identified on the points scale for each variable. The total points projected on the bottom scales indicate the probability of 3- and 5-year survival.](image)

In addition, to evaluate the predicting probability of our nomogram further, patients were stratified into 3 incremental risk level groups: low risk(0-12), medium risk(12-15) and high risk(>15)) which indicate different prognosis depending on X-tile program (Figure 6). A significant difference can be observed between different risk groups. The stratification strategy and result were summarized in supplementary figure (Supplementary Figure 1).

**Discussion**

In contrast to NCCN guidelines that recommended that pT3-4Nx GC patients undergo R0 resection should receive chemoradiotherapy, our research indicated that only chemotherapy contributed to superior prognosis rather than radiotherapy for...
MILN GC in Western practices. Thus these results suggested radiotherapy could be subtracted for this subgroup of patients. The survival analysis showed the CSS in radiotherapy subgroup was similar to that in non-radiotherapy subgroup, while CSS in chemotherapy subgroup was significantly better than that in non-chemotherapy subgroup. Further analyzing showed prognosis of radiotherapy-alone subgroup is not significantly different from that in non-adjuvant treatment subgroup, and the survival of chemoradiotherapy subgroup is similar to that in chemotherapy-alone subgroup. These results of the survival analysis indicated that the variate of radiotherapy could not improve survival. Furthermore, the Cox regression analysis confirmed that radiotherapy could not independently affect survival. Consistently, when the chemotherapy situation was totally the same between radiotherapy subgroup and non-radiotherapy subgroup by PSM, the survival of radiotherapy subgroup was inferior to that in non-radiotherapy subgroup. 

In consistent, recently, the CRITICS trial, the first trial to directly compare postoperative chemoradiotherapy with perioperative chemotherapy in patients with resectable GC, showed that postoperative chemoradiotherapy did not improve survival compared with resectable GC treated with adequate preoperative chemotherapy and surgery. After preoperative chemotherapy, 372 (95\%) of 393 patients in the chemotherapy subgroup and 369 (93\%) of 395 patients in the chemoradiotherapy subgroup proceeded to surgery. With a median follow-up of 61.4 months (IQR 43.3-82.8), mOS was 43 months (95% CI 31-57) in the chemotherapy subgroup and 37 months (30-48) in the chemoradiotherapy subgroup (HR 1.01, 95% CI 0.84 -1.22; p = 0.90). This result supported our hypothesis and finding in our

**Figure 5.** Validation of the nomogram for predicting 3- and 5-year cancer-specific survival (CSS) for lymph node metastasis-indolent locally advanced gastric cancer after gastrectomy. (A-B). Calibration plot. The x-axis represents the nomogram-predicted survival, and the y-axis represents actual survival measured by Kaplan-Meier analysis. The C-index for CSS was 0.699 (95% CI, 0.638-0.76). (C-D). Discrimination plot. The area under curve (AUC) values of the receiver operating characteristic (ROC) predicted the 3-, and 5-year CSS of the nomogram to be 0.708 and 0.761.
study that the survival benefit of chemoradiotherapy in Western practices may be attributed primarily to chemotherapy rather than to radiotherapy. The recent meta-analysis also showed that for advanced GC, radiochemotherapy displayed similar OS in comparison to chemotherapy alone.28 From the perspective of tumour heterogeneity, some T3-4 patients may have no LN metastasis, while some T1a-1b patients may confront extensive LN metastasis. Of course, the stage T3-4N0 GC are distinguished from the subgroup of biologically LN metastasis-active GC (T1a-1bN+) and could be conformed to our study demanding.

Also, the association between the extent of lymphadenectomy and survival benefit of radiotherapy is an interesting point worthin depth discussing to comprehend this research. Dikken et al. retrospectively compared survival and recurrence patterns to evaluate more intensified postoperative chemoradiotherapy than those from the Dutch Gastric Cancer Group Trial (DGCT), which randomly assigned patients between D1 and D2 lymphadenectomy.29 Survival and recurrence patterns of 91 patients with adenocarcinoma of the stomach who had received surgery followed by radiotherapy combined with fluorouracil and leucovorin (n = 5), capecitabine (n = 39), or capecitabine and cisplatin (n = 47) were analyzed and compared with the survival and recurrence patterns of 694 patients from the DGCT (D1, n = 369; D2, n = 325). The results revealed that the addition of postoperative chemoradiotherapy had a major impact on local recurrence in resectable gastric cancer with D1 LN dissection, while there was no difference in patients undergoing D2 dissection. Consistently, patients in the ARTIST-I and ARTIST-II trial,47 most of who underwent D2 LN dissection, did not benefit from the addition of radiotherapy. In addition, in the view of fundamental research, some vital researches have indicated epibiotic cancer cells in LNs resulting from the inadequate LN dissection of positive LNs would be active hubs for systemic tumor cell spreading and thus more prone to facilitating recurrence.32,33 Thus, radiotherapy could be an important complementary measure to reduce the potential cancer cells in LNs. Therefore, the benefit associated with chemoradiotherapy may be compensation for inadequate LN dissection (D1/D0) for nonspecific GC. While for LAGC patients who undergo standard radical D2 lymphadenectomy, which has been confirmed to achieve the maximum oncology efficacy for LAGC,34,35 or who are characterized as being MILN, the prognosis benefit of radiotherapy would be negative. And in our study, the MILN GC patients who mainly underwent D1/D0 LN dissection might be equal to the LN dissection effect of nonspecific GC patients mainly underwent D2 LN dissection. From this perspective, our results are reasonable and might be generalized.

Considering all these factors, the extent of LN dissection, biological LN status and primary tumor invasion should be taken into account when discussing and determining radiotherapy for GC. Furthermore, from the perspective of histology, the patients with intestinal-type GC are more likely to benefit from chemoradiotherapy than those with diffuse-type GC in the subgroup analysis of the INT0116 and ARTIST trials.10,19 Also, it has been acknowledged that therapeutic strategies in a multidisciplinary discussion for GC should be determined by
individual patient characteristics.\textsuperscript{28} Thus, identifying patients could benefit from radiotherapy or not is critical to subtract unnecessary treatment without undermining treatment effect. Thus, well-designed trials to determined tailored treatment for specific subgroups are in urgent.\textsuperscript{36}

The present study has several limitations that should be noted. This study was a retrospective study and the patients’ characteristics were unbalanced between groups. To compensate for this inherent limitation, we performed PSM with the variates that were unbalanced between groups and could independently affect the prognosis of MILN GC to improve the balance of baseline data. Notably, the significance of the difference in chemotherapy situation between radiotherapy subgroup and non-radiotherapy subgroup was changed from 0.001 to 1.000. Also, although we could identify whether the patients received chemotherapy or not, the SEER database did not provide information on the chemotherapy regimes, durations or the relationship with the surgery. Besides, MILN is a relevant concept, and the pathology result of LN-negative may guarantee MILN nature and the number of LNs examined after gastrectomy might affect the detection of LN-metastasis status.\textsuperscript{37-40} Thus, to compensate for this limitation, in our study, only patients with more than 15 LN examined were enrolled since this feature was defined as a surrogate for the evaluation of LN dissection.\textsuperscript{31,42}

Conclusions

MILN GC could not benefit from radiotherapy, which may only work as compensation for the poor surgical outcomes in LAGC patients with potential LN metastasis in Western practices. Chemoradiotherapy confers superior prognosis to MILN GC patients compared with surgery alone might only be attributed to chemotherapy rather than radiotherapy. This finding suggested that, contrary to NCCN guidelines, radiotherapy could be subtracted to reduce the side effects and treatment burden of radiotherapy for MILN GC patients. However, determining conclusions should be further verified in well-designed randomized trials.

Acknowledgments

We thank Prof. Jiang Yu, from Department of General Surgery and Prof. Liang Zhao from Department of Pathology, for their professional guidance and useful comments which have greatly improved the manuscript.

We also would like to thank the staff members of the National Cancer Institute and their colleagues across the United States and at Information management Services, Inc., who have been involved with the Surveillance, Epidemiology and End Results (SEER) Program. Finally, we would like to thank anonymous reviewers who gave valuable suggestion that has helped to improve the quality of the manuscript.

Author Contribution

Yunfei Zhi and Zhousheng Lin are authors contributed equally to the work.

Data Availability

Publicly available datasets were analyzed in this study. This data can be found here: https://seer.cancer.gov/data/.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

The SEER was public-use data: informed consent was waived. And our study was deemed exempt from institutional review board approval by NanFang Hospital, Southern Medical University.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was funded by the College Students’ Innovative Entrepreneurial Training Plan Program of Southern Medical University, Guangzhou. (Grant No.201912121290 and X202012121295)

ORCID iDs

Yunfei Zhi https://orcid.org/0000-0002-0084-6810

Xinhua Chen https://orcid.org/0000-0002-1879-4318

Supplemental Material

Supplemental material for this article is available online.

References

1. Thrift AP, El-Serag HB. Burden of gastric cancer. Clin Gastroenterol Hepatol. 2020;18(3):534-542. doi:10.1016/j.cgh.2019.07.045

2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424. doi:10.3322/caac.21492

3. Chen XH, Hu YF, Luo J, et al. The safety of esophagojejunostomy via a transorally inserted-anvil method vs extracorporeal anastomosis using a circular stapler during total gastrectomy for Siewert type 2 adenocarcinoma of the esophagogastric junction. Gastroenterol Rep. 2020;8(3):242-251. doi:10.1093/gastro/goz046

4. Yu J, Huang C, Sun Y, et al. Effect of laparoscopic vs open distal gastrectomy on 3-year disease-free survival in patients with locally advanced gastric cancer: the CLASS-01 randomized clinical trial. JAMA. 2019;321(20):1983-1992. doi:10.1001/jama.2019.5359

5. National HCOT. Chinese guidelines for diagnosis and treatment of gastric cancer 2018 (English version). Chin J Cancer Res. 2019;31(5):707-737. doi:10.21147/j.issn.1000-9604.2019.05.01

6. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29(33):4387-4393. doi:10.1200/JCO.2011.36.5908

7. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet
18. Lee J, Lim DH, Kim S, et al. Phase III trial comparing capecitabine and cisplatin versus concurrent chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastrooesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393(10184):1948-1957. doi:10.1016/S0140-6736(18)32557-1

19. Cunningham D, Allum WH, Stening SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11-20. doi:10.1056/NEJMoa055531

20. SEER. National Cancer Institute, Surveillance Epidemiology and End Results. 2019. Accessed November 15, 2019. http://seer.cancer.gov

21. Washington K. 7th edition of the AJCC cancer staging manual: stomach. Ann Surg Oncol. 2010;17(12):3077-3079. doi:10.1245/s10434-010-1362-z

22. R Core Team. R: A Language and Environment for Statistical Computing. RFoundation for Statistical Computing; 2019. Accessed November 14, 2019. https://www.R-project.org/

24. Therneau TM, Grambsch PM. Modeling Survival Data: Extending the Cox Model. Springer; 2000. ISBN 0-387-98784-3.

25. Frank E Harrell Jr. RMS: Regression Modeling Strategies. R package version5.1-4. 2019. https://CRAN.R-project.org/package=rms

26. Harrell FEJr, with contributions from Charles Dupont and many others. Hmisc: Harrell Miscellaneous. R package version 4.3-0. 2019.

27. Cats A, Jansen E, van Grieken N, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018;19(5):616-628. doi:10.1016/S1470-2045(18)30132-3

30. Lawson JD, Sicklick JK, Fanta PT. Gastric cancer. 2015;14(10):1286-1312. doi:10.6004/jnccc.2016.0137

31. Deng J, Liu J, Wang W, et al. Validation of clinical significance of examined lymph node count for accurate prognostic evaluation of gastric cancer for the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system. Chin J Cancer Res. 2018;30(5):477-491. doi:10.21147/j.issn.1000-9604.2018.05.01

32. Brown M, Assen FP, Leithner A, et al. Lymph node blood vessels provide exit routes for metastatic tumor cell dissemination in mice. Science. 2018;359(6382):1408-1411. doi:10.1126/science.aal3662

33. Pereira ER, Kedrin D, Seano G, et al. Lymph node metastases can invade local blood vessels, exit the node, and colonize distant organs in mice. Science. 2018;359(6382):1403-1407. doi:10.1126/science.aal3622

34. Songun I, Putter H, Kransberg EM, Sasaki M, van de Velde CJ. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11(5):439-449. doi:10.1016/S1470-2045(10)70070-X

35. Degiuli M, De Manzoni G, Di Leo A, et al. Gastric cancer: current status of lymph node dissection. World J Gastroenterol. 2016;22(10):2875-2893. doi:10.3748/wjg.v22.i10.2875. doi:10.3748/wjg.v22.i10.2875
36. Chen X, Liu H, Li G, Yu J. Implications of clinical research on adjuvant chemotherapy for gastric cancer: where to go next? *Chin J Cancer Res*. 2019;31(6):892-900. doi:10.21147/j.issn.1000-9604.2019.06.05

37. Zhu Y, Chen XH, Li TT, et al. Method and experience of lymph node examination after gastrectomy with D2 lymphadenectomy for gastric cancer. *Chin J Gastrointest Surg*. 2019;22(8):796-800. doi:10.3760/cma.j.issn.1671-0274.2019.08.018

38. Jiang L, Yao Z, Zhang Y, et al. Comparison of lymph node number and prognosis in gastric cancer patients with perigastric lymph nodes retrieved by surgeons and pathologists. *Chin J Cancer Res*. 2016;28(5):511-518. doi:10.21147/j.issn.1000-9604.2016.05.06

39. Bai H, Deng J, Zhang N, et al. Predictive values of multidetector-row computed tomography combined with serum tumor biomarkers in preoperative lymph node metastasis of gastric cancer. *Chin J Cancer Res*. 2019;31(3):453-462. doi:10.21147/j.issn.1000-9604.2019.03.07

40. Chen X, Chen Y, Hu Y, et al. The methods of lymph node examination make a difference to node staging and detection of N3b node status for gastric cancer. *Front Oncol*. 2020;10:123. doi:10.3389/fonc.2020.00123

41. Seevaratnam R, Bocicariu A, Cardoso R, et al. How many lymph nodes should be assessed in patients with gastric cancer? A systematic review. *Gastric Cancer*. 2012;15(Suppl 1):S70-S88. doi:10.1007/s10120-012-0169-y

42. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable gastric cancer of advanced stage. *Ann Surg Oncol*. 2007;14(2):317-328. doi:10.1245/s10434-006-9218-2