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Research article

Neoadjuvant versus adjuvant radiotherapy for resectable locally advanced gastric cancer: A SEER population analysis

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ABSTRACT

Background: There is a lack of evidence on whether resectable locally advanced gastric cancer (LAGC) patients could benefit from neoadjuvant or adjuvant radiotherapy (RT).
Methods: Patients with surgically diagnosed LAGC from 2004 to 2015 were retrieved from the SEER database. Kaplan-Meier method and the log-rank test were used to evaluate survival analysis between neoadjuvant and adjuvant RT. Univariate Cox regression was used to evaluate the hazard ratio (HR) and 95 % confidence interval (CI).
Results: A total of 4790 LAGC patients who treated with surgery and RT were identified, including 3187 patients with intestinal subtype and 1603 patients with diffuse subtype. For patients with both intestinal and diffuse subtypes, median cancer-specific survival (mCSS) was better with adjuvant RT or neoadjuvant RT. Moreover, patients benefited more from adjuvant RT than neoadjuvant RT (intestinal subtype: mCSS 49 vs. 36 months, $P < 0.001$; diffuse subtype: mCSS 32 vs. 26 months, $P = 0.050$). Further analyses showed that patients with intestinal subtype and $T_{1\text{-}2}N^+$, T_3N^-, T_3N^+ subgroups, as well as patients with diffuse subtype and $T_{1\text{-}2}N^+$ and T_3N^+ subgroups benefited more from adjuvant RT than those with neoadjuvant RT. Patients in the diffuse subtype and T_3N^- subgroups also tended benifit from adjuvant RT and survive. There was no difference in survival between the T_4N^- and T_4N^+ subgroups of the two subtypes. After propensity score matching, subgroup analysis identified an improved survival in favor of adjuvant RT in the age ≥65 years and female subgroups in diffuse subtypes and T_4N^+ patients.
Conclusions: For patients with resectable LAGC in the $T_{1\text{-}2}N^+$, T_3N^-, T_3N^+ clinical subgroups, adjuvant RT yields more benefits than neoadjuvant RT or no RT, which is worthy of prospective clinical trial.

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1. Introduction

Gastric cancer (GC) is one of the most common malignant tumors in the world. According to Global Cancer Statistics 2020, there were 1,033,701 new cases of GC in 2018, accounting for 5.7 % of all newly diagnosed cancers [1]. However, the mortality rate of GC is as high as 8.2 %, ranking third in the world, with a total of 782,685 deaths. In the United States (US), 27,000 new cases are expected in 2020 [1]. Due to the lack of typical clinical symptoms, more than 75 % of newly diagnosed GC patients are in advanced stage. Patients with advanced disease often have of muscle layer or lymph node involvement, and the survival rate is low [2].

Abbreviation list

GC	Gastric cancer (GC)
US,	United States
RT	radiotherapy
LAGC	locally advanced gastric cancer
CRT	chemoradiotherapy
SEER	Surveillance, Epidemiology, and End Results
GEJ	gastroesophageal junction
ICD-O-3	International Classification of Diseases for Oncology, Version 3
AJCC	American Joint Committee on Cancer
CSS	cancer-specific survival
HR	hazard ratio
CI	confidence interval
PSM	propensity score matching
mCSS	median cancer-specific survival
OS	overall survival
LRFS	local recurrence-free survival
DFS	disease-free survival
MSI	microsatellite instability
PD-L1	programmed death-ligand 1
NCCN	National Comprehensive Cancer Network
ESMO	European Society for Medical Oncology

Surgery is the most commonly used treatment for GS patients, but the survival outcome of surgery alone is poor. Especially in patients with node-positive cancer, the 5-year survival rate is only about 30 % [3]. Therefore, additional perioperative treatment strategies such as radiotherapy (RT) and/or chemotherapy are considered to improve survival outcomes, and a few studies have demonstrated the survival benefit of perioperative treatment [4–9]. A study from China found that local recurrence-free survival (LRFS) was improved with intensity-modulated radiotherapy plus chemotherapy (IMRT-C) after D2 lymphadenectomy for locally advanced GC (LAGC) (T3 and/or node-positive) [9]. The RTOG 9904 study in the US showed a good effect of preoperative chemoradiotherapy (CRT) for LAGC [10]. According to INT0116 study, National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant chemoradiotherapy as the standard treatment after radical gastrectomy for gastric cancer [4,5,11]. According to the European Society for Medical Oncology (ESMO) guidelines, RT is not recommended for patients undergoing R0 resection and perioperative chemotherapy. For patients with R1 resection but wirhout preoperative chemotherapy and D2 lymph node dissection, RT could be an alternative adjuvant therapy, but it is not the standard treatment [12]. The latest edition of NCCN guidelines recommends perioperative chemotherapy for patients with T_2 or above and all N stages (category 1). And perioperative CRT is recommended as level 2B. However, adjuvant CRT is not recommended [11].

At present, only a few studies directly compared the role of preoperative and postoperative RT in patients with LAGC, and have yielded conflicting results [13–16]. Even, one study suggested that RT should not be added to perioperative or adjuvant chemotherapy [17]. For patients with resectable LAGC, preoperative RT or postoperative RT is still controversial. Therefore, this study, based on a large sample population from the Surveillance, Epidemiology, and End Results (SEER) database, was designed to investigate the role of RT in patients with resectable LAGC patients and to identify eligible patients.

2. Methods

2.1. Study participants

Patients with LAGC diagnosed between 2004 and 2015 were identified from SEER 17 registries, Nov 2021 submission (2000–2019), representing approximately 26.5 % of the US population. The inclusion and exclusion criteria are presented in Fig. 1. Patients with gastroesophageal junction (GEJ) cancer were not included in this study. The last follow-up time was Dec 31, 2019. Hence, we limited the sample to patients diagnosed until 2015 to allow for at least 4 years of follow-up time.

2.2. Variables

All patients with resected LAGC were histologically classified as intestinal subtype and diffuse subtype according to Lauren classification and the codes of International Classification of Diseases for Oncology, Version 3 (*ICD-O-3*) [18]. The intestinal type included 8144/3 (adenocarcinoma, intestinal type), 8140/3 (adenocarcinoma, not otherwise specified), 8010/3 (carcinoma, not otherwise specified), 8211/3 (tubular adenocarcinoma). And the diffuse subtype included 8145/3 (carcinoma, diffuse type), 8490/3 (signet ring cell carcinoma), 8142/3 (linitisplastica).

The original American Joint Committee on Cancer (AJCC) TNM staging system for patients diagnosed between 2004 and 2009 was the 6th version, and that was the 7th version for patients diagnosed between 2010 and 2015. The tumor stages of all patients were reevaluated according to the AJCC 8th TNM staging system of GC and were divided into five clinical subgroups, i.e. $T_{1\text{-}2}N^{+}$, T_3N^{-}, T_3N^{+}, T_4N^{-}, and T_4N^{+} subgroups.

The other variables included age (<65 years, ≥65 years), sex (male, female), race (white, black, others), year of diagnosis (2004–2009, 2010–2015), tumor grade (grade I-II, grade III-IV, unknown), systemic treatment (No, Yes), surgery type (partial gastrectomy, near total/total gastrectomy, gastrectomy, not other specified), and RT (neoadjuvant, adjuvant).

2.3. Treatment interventions for LAGC

All LAGC patients who received both RT and surgery were classified into 2 groups according to sequence of external-beam RT and surgery in the initial treatment course. The neoadjuvant group was composed of patients who received RT prior to surgery, and the adjuvant group was composed of patients who received RT after surgery. Patients who received non-external-beam RT were excluded for analysis.

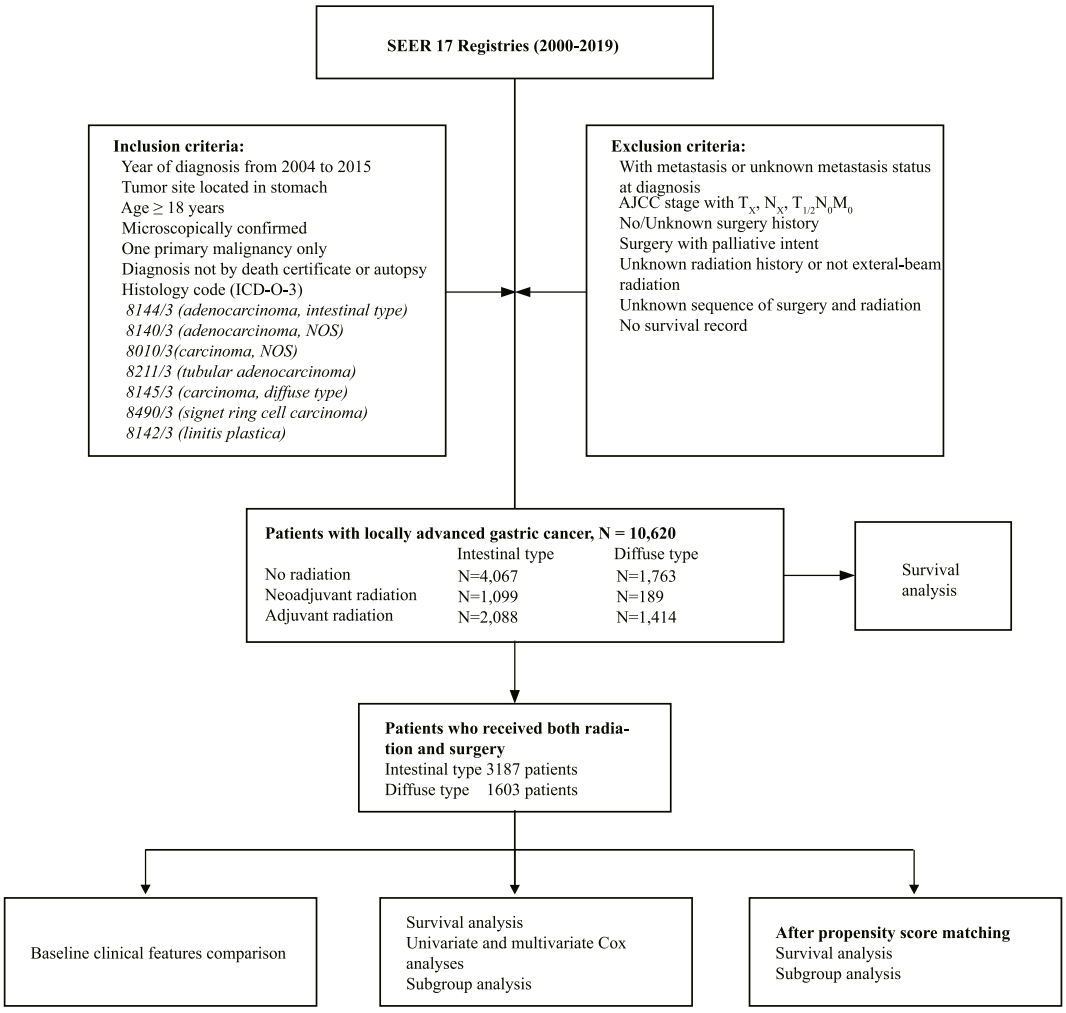

Fig. 1. A flow chart of the study design.

2.4. Outcome

The outcome of this study was the cancer-specific survival (CSS), which was defined as the follow-up time from diagnosis to death due to LAGC. Patients who were alive or died due to other reasons at the last follow-up were regarded as censored cases. Compared to overall survival, the CSS could reduce the impact of deaths caused by other reasons, such as chronic diseases and accident. The CSS could better identify the role of RT on LAGC.

2.5. Study design and statistical analysis

First, baseline clinical features of all patients with intestinal and diffuse subtypes were described as frequencies and compared by Pearson's X^2 test. Next, survival analyses were performed between patients who received neoadjuvant RT and patients who received adjuvant RT, both in intestinal and diffuse subtypes, and in the clinical subgroups accordingly. The survival was assessed by the Kaplan-Meier method and the log-rank test. Univariate Cox regression analysis was used to evaluate the hazard ratio (HR) and 95 % confidence interval (CI). Then, subgroup analysis was performed to further explore significant subgroups affecting the CSS. Last, the propensity score matching (PSM) method was used to balance the clinical features between neoadjuvant RT and adjuvant RT groups, and further survival analysis and subgroup analysis were performed after PSM to explore significant subgroups. For the PSM analysis, each patient received neoadjuvant RT was matched with one patient received adjuvant RT, and clinical features between the matched groups were compared. The variables used for PSM analysis included age, sex, race, year of diagnosis, tumor grade, systemic treatment, and surgery type.

In addition, univariate and multivariate Cox analyses were performed to determine the prognostic factors associated with CSS in patients with intestinal and diffuse subtypes, respectively. All patients were identified with SEER*Stat software (version 8.4.0.1; https://seer.cancer.gov/seerstat/). All statistical analyses were performed with R software (version 4.2.1; http://www.rproject.org/). The related R packages included CBCgrps, rms, survival, survminer, and MatchIt. Two-sided p-value <0.05 was considered to indicate statistical significance.

Table 1
Baseline clinical features comparison between patients with intestinal and diffuse subtypes, all patients were treated with both radiation and surgery.

Variables	Total, N = 4790 (%)	Diffuse, N = 1603 (%)	Intestinal, N = 3187 (%)	X^2	*P-value*
Age (years)				*71.98*	*< 0.001*
< 65	2809 (59)	1077 (67)	1732 (54)		
≥ 65	1981 (41)	526 (33)	1455 (46)		
Sex				*88.32*	*< 0.001*
Male	3237 (68)	873 (54)	2364 (74)		
Female	1553 (32)	730 (46)	823 (26)		
Race				*29.70*	*< 0.001*
White	3288 (69)	1021 (64)	2267 (71)		
Black	540 (11)	196 (12)	344 (11)		
Others	962 (20)	386 (24)	576 (18)		
Year of diagnosis				*10.80*	*0.001*
2004–2009	2402 (50)	858 (54)	1544 (48)		
2010–2015	2388 (50)	745 (46)	1643 (52)		
Clinical subgroups				*29.11*	*< 0.001*
$T_{1\text{-}2}N^+$	723 (15)	206 (13)	517 (16)		
T_3N^-	522 (11)	141 (9)	381 (12)		
T_3N^+	1966 (41)	558 (35)	1408 (44)		
T_4N^-	256 (5)	102 (6)	154 (5)		
T_4N^+	1323 (28)	596 (37)	727 (23)		
Tumor grade				*80.64*	*< 0.001*
Grade I-II	1208 (25)	42 (3)	1166 (37)		
Grade III-IV	3381 (71)	1492 (93)	1889 (59)		
Unknown	201 (4)	69 (4)	132 (4)		
Systemic treatment				*1.09*	*0.770*
No	265 (6)	86 (5)	179 (6)		
Yes	4525 (94)	1517 (95)	3008 (94)		
Surgery type				*85.88*	*< 0.001*
Partial gastrectomy	3129 (65)	1012 (63)	2117 (66)		
Near total/total gastrectomy	1212 (25)	508 (32)	704 (22)		
Gastrectomy, not other specified	449 (9)	83 (5)	366 (11)		
Radiotherapy				*78.24*	*< 0.001*
Neoadjuvant	1288 (27)	189 (12)	1099 (34)		
Adjuvant	3502 (73)	1414 (88)	2088 (66)		

3. Results

3.1. Patient clinical features

A total of 10,620 patients with LAGC were identified. Among them, 4790 patients received surgery and RT in the initial treatment course, including 3187 patients with intestinal subtype and 1603 patients with diffuse subtype. The clinical features of these patients are presented in Table 1. Compared to patients with diffuse subtype, patients with intestinal subtype had relatively higher proportions of older population (age ≥65 years, 46 vs. 33 %, $P < 0.001$), male patients (74 vs. 54 %, $P < 0.001$), and white population (71 vs. 64 %, $P < 0.001$). The proportions of T_4 stage (28 vs. 43 %, $P < 0.001$) and tumor grade III-IV (59 vs. 93 %, $P < 0.001$) in patients with intestinal subtype were lower. Patients with diffuse subtype were more prone to receive adjuvant RT (88 vs. 66 %, $P < 0.001$). The proportions of systemic treatment in the two groups were similar (95 vs. 94 %, $P = 0.770$).

3.2. Survival analysis

Survival analyses between patients who received RT (N = 4790) and no RT (N = 5830) were performed both in intestinal and diffuse groups. The results turned out that patients could benefit more from both receiving adjuvant RT and receiving neoadjuvant RT compared to patients who received no RT (Fig. 2).

Further, survival analyses between patients with neoadjuvant RT and adjuvant RT were performed. For the patients with intestinal subtype, the median CSS (mCSS) was better in those who received adjuvant RT compared to those who received neoadjuvant RT (mCSS 49 vs. 36 months; HR 1.21, 95 % CI 1.10–1.33, $P < 0.001$; Fig. 3A). The adjusted HR after univariate and multivariate analyses remained higher for patients who received neoadjuvant RT (Table S1). In addition to that, race, clinical subgroups, tumor grade were prognostic factors associated with CSS (Table S1). For the patients with diffuse subtype, a better mCSS was also found for those who received adjuvant RT (mCSS 32 vs. 26 months; HR 1.20, 95 % CI 1.00–1.44, $P = 0.050$; Fig. 3B). The adjusted HR also remained higher for these patients (Table S2). And the significantly associated prognostic factors included age, race, year of diagnosis, clinical subgroups, and surgery type (Table S2). Notably, systemic treatment demonstrated no impact on CSS both in patients with intestinal and diffuse subtypes.

Moreover, survival analyses considering the tumor stage and nodal status were performed. Patients with intestinal subtype and $T_{1\text{-}2}N^+$, T_3N^-, T_3N^+ stages showed longer CSS from adjuvant RT compared to neoadjuvant RT (Fig. 4A–C). While for patients with T_4N^- and T_4N^+ stages, no survival difference was found (Fig. 4D–E). For patients with diffuse subtype, a better mCSS was found for those with $T_{1\text{-}2}N^+$ and T_3N^+ stages and receiving adjuvant RT (Fig. 5A and B), but not in T_3N^-, T_4N^- and T_4N^+ stages (Fig. 5C, 5D-E).

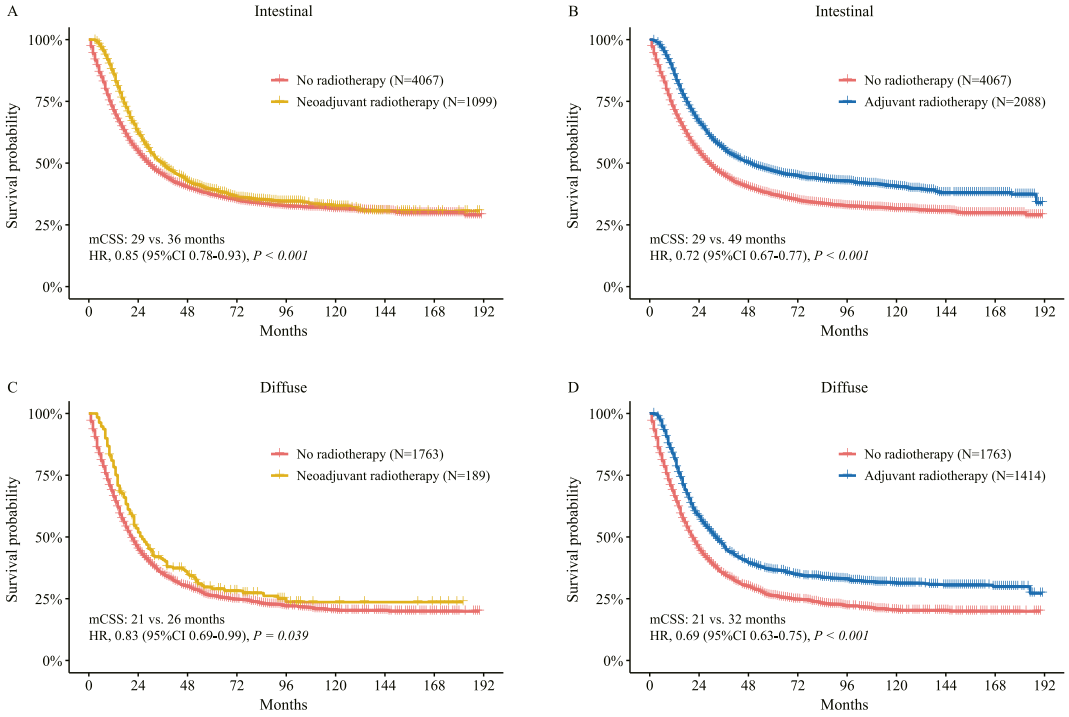

Fig. 2. Kaplan–Meier curves for CSS. A) Between intestinal patients with neoadjuvant and no radiotherapy, B) Between intestinal patients with adjuvant and no radiotherapy, C) Between diffuse patients with neoadjuvant and no radiotherapy, D) Between diffuse patients with adjuvant and no radiotherapy. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

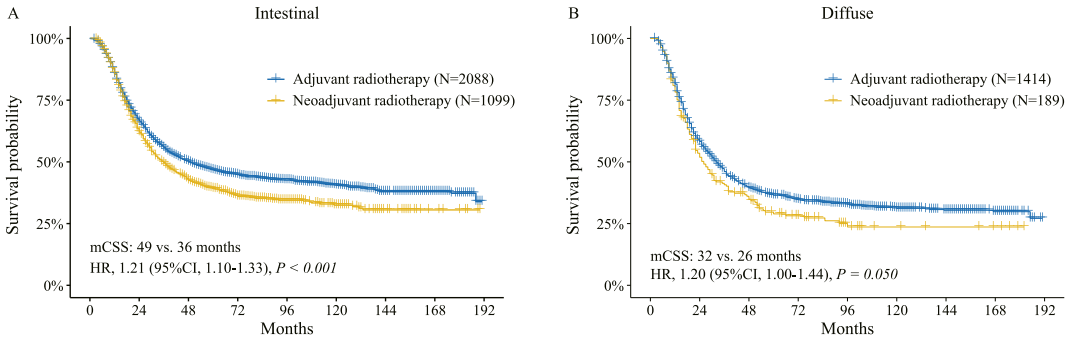

Fig. 3. Survival analysis between patients who received neoadjuvant and adjuvant radiotherapy for A) intestinal subtype, and B) diffuse subtype. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval.

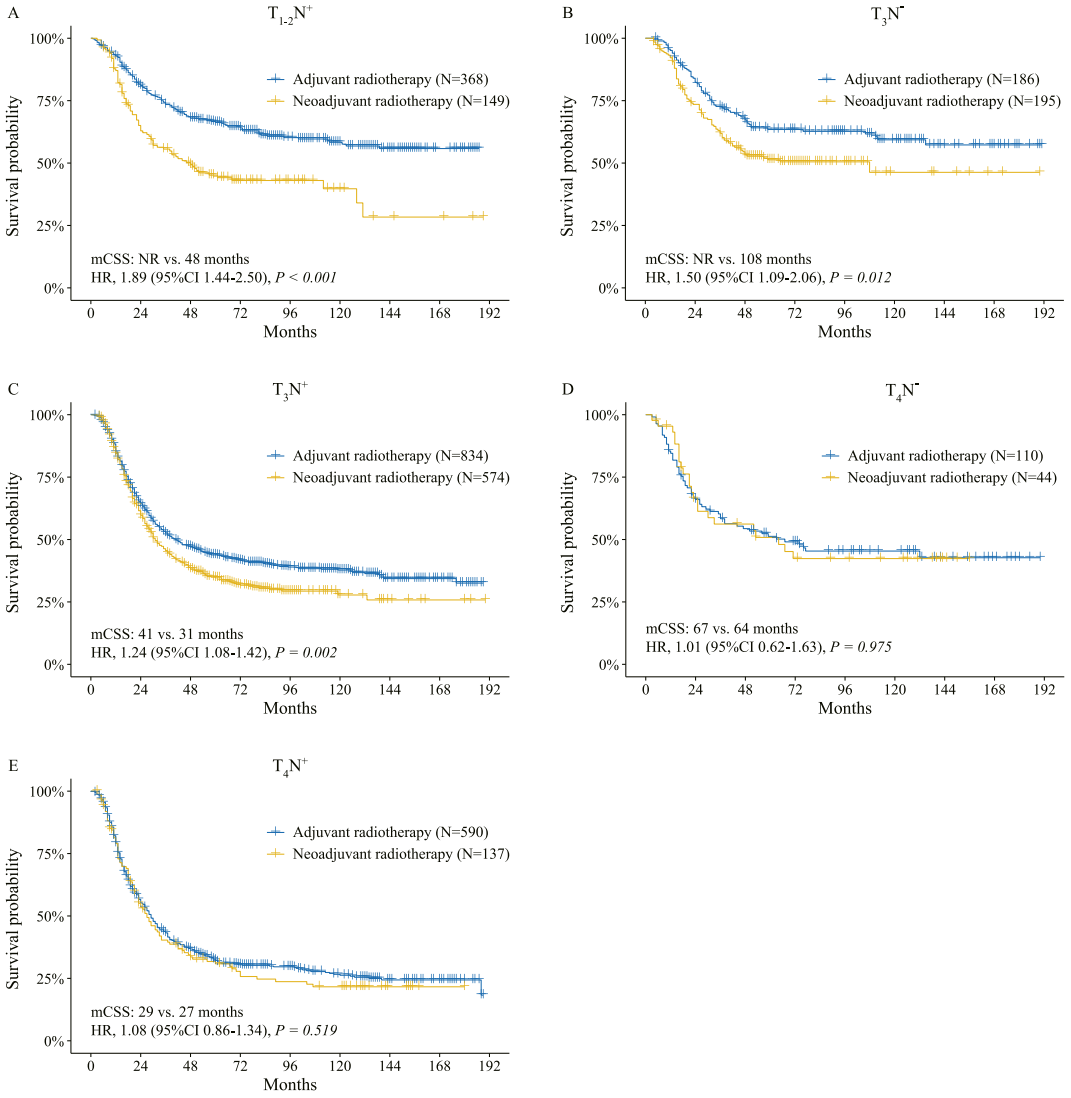

Fig. 4. Kaplan–Meier curves for cancer-specific survival among patients with intestinal subtype and A) $T_{1\text{-}2}N^+$ subgroup, B) T_3N^- subgroup, C) T_3N^+ subgroup, D) T_4N^- subgroup, and E) T_4N^+ subgroup. CSS, cancer-specific survival; NR, not reach; HR, hazard ratio; CI, confidence interval.

Furthermore, subgroup analyses in clinical subgroups with no survival difference were performed, i.e. patients with intestinal subtype and T_4N^-, T_4N^+ subgroups, and patients with diffuse subtype and T_3N^-, T_4N^+ subgroups. While no significantly positive result was found (Figs. S1–4). Subgroup analysis in patients with diffuse subtype and T_4N^- stage was not performed because of too few patients in this clinical subgroup.

3.3. Survival and subgroup analyses after propensity score matching

Then, PSM analysis was performed to further explore subgroups which might benefit from adjuvant RT or neoadjuvant RT. After PSM, all clinical features were balanced. The details are presented in Tables S3–6. The survivals remained no significant difference between adjuvant RT and neoadjuvant RT in patients with intestinal subtype and T_4N^-, T_4N^+ subgroups, and patients with diffuse subtype and T_3N^-, T_4N^+ subgroups (Fig. 6). Further subgroup analysis for patients with diffuse subtype and T_4N^+ subgroup found that, an improvement in survival favored adjuvant RT in subgroups of age ≥65 years, female, and year of diagnosis 2010–2015 (Fig. 7). Subgroups analyses for patients with intestinal subtype and T_4N^-, T_4N^+ subgroups, and patients with diffuse subtype and T_3N^- subgroup still did not demonstrate significantly positive result (Figs. S5–7).

4. Discussion

The best treatment strategy for LAGC is perioperative comprehensive treatment, including chemotherapy, radiotherapy, novel

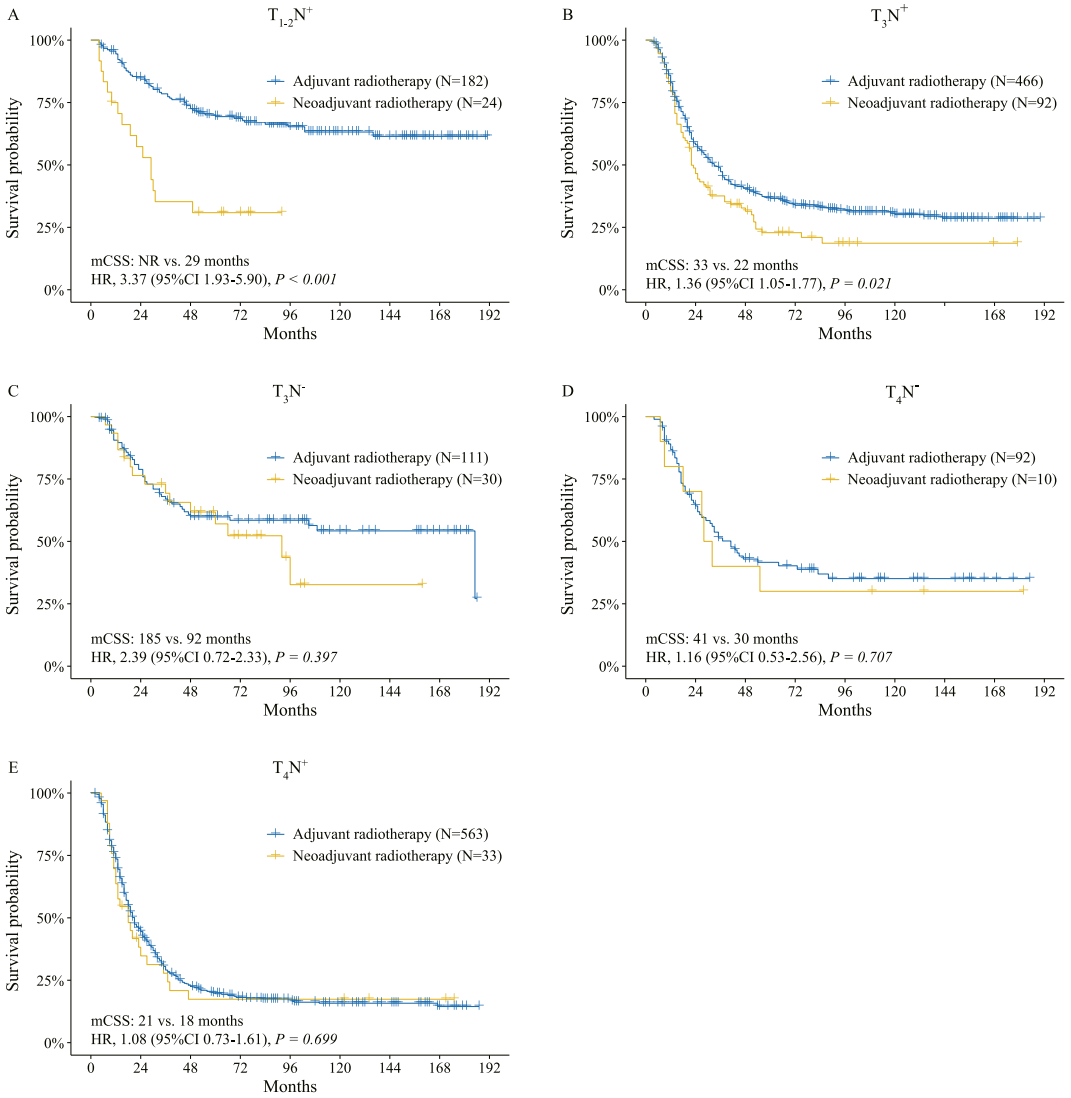

Fig. 5. Kaplan–Meier curves for cancer-specific survival among patients with diffuse subtype and A) $T_{1\text{-}2}N^+$ subgroup, B) T_3N^- subgroup, C) T_3N^+ subgroup, D) T_4N^- subgroup, and E) T_4N^+ subgroup. CSS, cancer-specific survival; NR, not reach; HR, hazard ratio; CI, confidence interval.

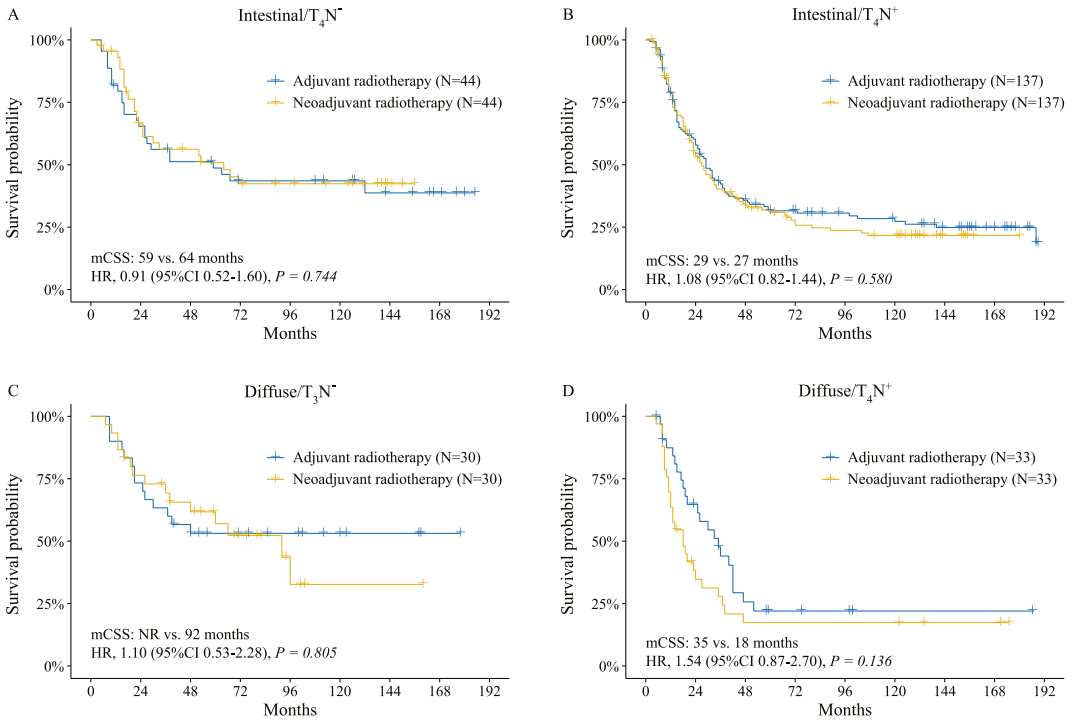

Fig. 6. Kaplan–Meier curves for cancer-specific survival after propensity score matching. CSS, cancer-specific survival; HR, hazard ratio; CI, confidence interval; NR, not reach.

molecular drugs and immunotherapy [1,19]. A few studies support that surgery plus RT can improve the survival of patients with gastric cancer. The INT0116 trial found that OS was superior with adjuvant CRT versus surgery alone in GS patients with stage IB to IV/M0 (36 vs 27 months, $P = 0.005$) [4]. In addition, the median 10-year follow-up of INT0116 demonstrated a sustained efficacy and survival benefit for GC patients treated with adjuvant CRT [5]. However, patients with GEJ cancer was not excluded in this study, which may affect the prognosis to some extent. Therefore, adjuvant CRT is recommended for resected GC with a high risk of recurrence (such as primaries T3 or greater and/or node-positive). A retrospective study in the SEER database found that in patients with lymph node-positive GC, patients who received adjuvant RT had a significantly improved 5-year overall survival (OS) compared with those who did not receive RT (30.4 vs 21.4 %, $P < 0.001$) [6]. A phase III clinical trial in South Korea showed that in patients with stage III GC, adjuvant CRT significantly improved 5-year LRFS and disease-free survival (DFS) compared with adjuvant chemotherapy alone (LRFS, 93.2 vs. 66.8 %, $P = 0.014$; DFS,73.5 vs 54.6 %, $P = 0.056$) [7]. But another study (ARTIST), also from South Korea, showed different results. A total of 458 patients with GC who underwent D2 lymph node dissection were randomly divided into capecitabine + cisplatin (XP) group (N = 228 cases) and XP + RT group (N = 230). The results showed that compared with XP alone, XP combined with RT did not prolong the 3-year DFS rate (74.2 vs 78.2 %, $P = 0.086$). However, in a subgroup analysis of pathologic lymph node-positive patients, DFS was significantly better with XP plus RT than with XP alone (3-year DFS rate, 77.5 vs. 72.3 %, $P = 0.036$) [38]. In this study, we found that in patients with both intestinal and diffuse LAGC, both neoadjuvant RT and adjuvant RT benified LAGC patients compared with no RT. There may be two mechanisms by which radiotherapy improves the survival of patients with radical gastrectomy. On one hand, preoperative radiotherapy can lower down tumor staging, make unresectable patients eligible for surgery, and improve the R0 resection rate [13]. On the other hand, radiotherapy helps to control micrometastasis [2]. Although both prospective randomized studies and retrospective big data demonstrated the value of radiotherapy, the recent ARTIST 2 study, which involved 546 patients with curatively D2-resected, stage II/III, node-positive GC, showed no DFS difference between adjuvant SOXRT cohort (S-1 plus oxaliplatin plus RT) and SOX cohort (3-year DFS rate, 72.8 vs. 74.3 %, HR 0.971, $P = 0.879$) [20].

Our results demonstrate that patients with intestinal subtype and diffuse types have different significantly associated prognostic factors. This may be related to the differences in epidemiological trends, etiology and pathogenesis and modes of disease progression and metastasis between the two subtypes [21–23]. Diffuse LAGC patients subtype are more likely to have peritoneal metastasis, rapid progression, and worse outcome [24].

Currently, only a few studies directly compared the survival between neoadjuvant and adjuvant RT in patients with resectable disease (Table S7). A retrospective study included patients with nonmetastatic gastric adenocarcinoma resected between 1988 and 2008 from SEER database [16]. For stage I patients, those who underwent surgery only exhibited the best CSS. For stage II, III, and IV patients, surgery combined with CRT was more beneficial than other treatment options. These results partially support our findings. However, no further subgroup analysis was performed. Yang's retrospective study includeded 82 patients with gastric or GEJ cancer and stage III/IVa disease (i.e., $T_{3\text{-}4a}N^{+}M_0$ or $T_{4b}N_xM_0$) in the preoperative CRT group and 463 patients with postoperativeCRT. After

Variable	HR (95% CI)	*P-value*
Age (years)		
< 65	1.26 (0.66–2.40)	*0.484*
≥ 65	4.84 (1.16–20.23)	*0.031*
Sex		
Male	1.19 (0.56–2.55)	*0.646*
Female	2.92 (1.20–7.08)	*0.018*
Race		
White	1.39 (0.76–2.53)	*0.288*
Black	Not available	
Others	Not available	
Year of diagnosis		
2004–2009	0.81 (0.33–1.95)	*0.633*
2010–2015	3.32 (1.50–7.36)	*0.003*
Tumor grade		
Grade I–II	Not available	
Grade III–IV	1.67 (0.94–2.95)	*0.079*
Unknown	Not available	
Systemic treatment		
No	Not available	
Yes	1.53 (0.86–2.72)	*0.148*
Surgery type		
Partial gastrectomy	2.06 (0.89–4.75)	*0.090*
Near total/total gastrectomy	1.78 (0.76–4.20)	*0.185*
Gastrectomy, NOS	0.18 (0.02–1.84)	*0.150*

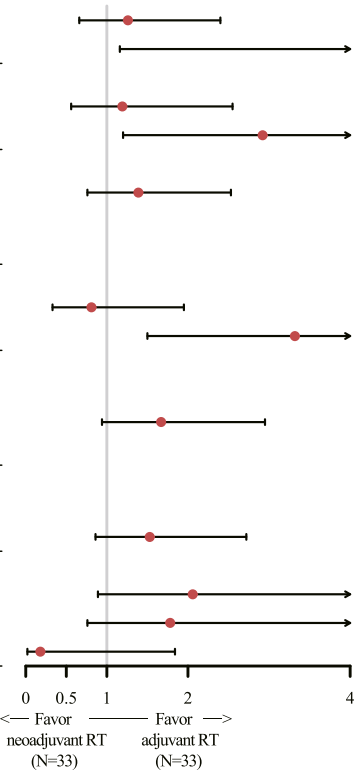

Fig. 7. A forest plot displaying the HR and 95 % CI of each variable affecting survival among patients with diffuse subtype and T_4N^+ subgroup after propensity score matching. The square and line segments represent the HRs and 95 % CI, and HR > 1.000 indicates a higher risk. HR, hazards ratio; CI, confidence interval; NOS, not other specified; RT, radiotherapy.

PSM, the preoperative group had better OS and DFS, better treatment compliance, and similar surgical complications compared with the preoperative group [14]. Similarly, Li and colleagues also found that patients with stage $T_{3/4}$ and/or N positive gastric cancer treated with surgery and preoperative CRT had better efficacy and survival than patients treated with surgery and postoperative CRT [13]. These results are in dispute with our findings. The possible reasons can be explained as follows. Firstly, for Yang's study, they also included a subset of patients with GEJ cancer who were confirmed to be benefit from preoperative RT with clear evidences [25,26]. This may have led to a better survival in patients with preoperative CRT. Secondly, the accuracy of preoperative clinical staging of GC patients is challenging in practice. It has been reported that about 30 % of patients were found to have peritoneal metastasis during operation, while clinical M0 stage was diagnosed by imaging at the time of diagnosis [27]. These understaged patients may progress rapidly. This reason may partially explain our results, but not those of these two studies. Thirdly, since the preoperative CRT could reduce the tumor stage and improve the R0 resection rate. Patients can benefit more from preoperative CRT in the early stage of the treatment. However, the long-term survival benefit of the two treatment regimens could not be fully assessed from these two studies, which had limited follow-up. Besides, the sample sizes of the two studies were limited, which may have introduced potential bias. The results of network meta-analysis demonstrated that preoperative CRT and postoperative CRT had no significant effect on OS [15]. The retrospective design of these studies may have led to the contradictory results. Therefore, further prospective randomized clinical trials are warranted to address this issue.

Our study has certain strengths and implications for clinical practice. First, unlike most studies involving GEJ cancer, our study included only GC patients. This helped to reduce the heterogeneity of the study population. Second, this study is the first to directly compare the effects of neoadjuvant versus adjuvant RT on survival in patients with LAGC patients. The results showed that adjuvant RT was superior to neoadjuvant RT for patients with $T_{1\text{-}2}N^+$, T_3N^-, T_3N^+ intestinal and diffuse LAGC. Especially for the $T_{1\text{-}2}N^+$ and T_3N^- subgroups, the survival benefit of adjuvant RT were significant. The P-value of T_3N^- subgroup comparison of diffuse LAGCs was not statistically significant, which may be related to the limited sample size of diffuse LAGC patients who received neoadjuvant RT. Therefore, base on our findings, adjuvant RT, is recommended over neoadjuvant RT or no RT for LAGC patients with$T_{1\text{-}2}N^+$, T_3N^-, T_3N^+. However, the benefits of adjuvant RT in diffuse LAGC patient with T_3N^- still need to be further confirmed by studies with a larger sample size. However, for patients with T_4 stage, there was no survival difference between neoadjuvant and adjuvant RT regardless of lymph node status. Further subgroup analysis after PSM suggested that among diffuse subtype and T_4N^+ patients, potential those who were ≥65 years old, female, or diagnosed between 2010 and 2015 might benefit from adjuvant RT. There is some

heterogeneity in T4 patients, which should be interpreted with caution. According to the AJCC 8th edition for GC, $T_{4a}N^{-}$, $T_{4a}N^{+}$, $T_{4b}N^{-}/N^{+}$ correspond to stage IIB, III, IVA, respectively. In this study, limited to the sample size and the conversion of different AJCC versions, we did not stratitize T_4 further into T_{4a} and T_{4b}.

Moreover, an intriguing result was found in this study. T_3N^{+} patients had relatively worse CSS compared with T_4N^{-} patients (Fig. 2C and D). A previous study has demonstrated that lymph node positivity is an independent prognostic factor in GC patients [28]. In this study, the T_4N^{-} clinical subgroup consisted of more $T_{4a}N^{-}$ (IIB) but less $T_{4b}N^{-}$ (IVA). These factors may have contributed to the lower survival in the T_3N^{+} (III) subgroup. Of note, factor systemic treatment was not associated with prognosis in this study. This may be due to the fact that most patients, approximately 94 %, received systemic treatment during the initial treatment course.

A series of studies have identified subgroups of potential benefit from adjuvant RT. A secondary analysis of the ARTIST trial found that the CRT was effective only in LAGC patients with complete D2-resection but without preoperative sarcopenia [29]. In addition, the team found that patients with D2-resected non-mesenchymal LAGC may benefit more from CRT [21]. Moreover, age and absolute lymphocyte count may also have potential impact on the efficacy of CRT [30,31].

In addition to the shortcomings mentioned in the above discussion, some limitations should be acknowledged. First, we did not divide lymph node status into N_1, N_2, N_{3a}, N_{3b}. When we converted the 6th edition AJCC staging system to the 8th edition, we could not estimate whether the 6th edition N_1 stage was the 8th edition N_1 or N_2 stage because we did not have data on the exact number of postoperative positive lymph nodes. Second, the detailed regimes for systematic treatment are not provided in the SEER database. Previous studies have shown that trastuzumab, nivolumab, and pembrolizumab are promising in clinical trials for the treatment of patients with GC [11,32–35]. Besides, there is insufficient documentation in the SEER database regarding systemic treatment and surgery sequence. These may hinder the search for significant factors associated with survival and may lead to a potential bias in determining the role of RT in patients with resectable LAGC. Since then, according to the latest NCCN clinical practice guidelines in oncology (Version 2.2022) and ESMO clinical practice guidelines, adjuvant CRT was recommended only for GC patients without D2 lymph node dissection [11,12]. Since 2010, D2 lymphadenectomy has been the recommended surgical procedure for patients with resectable (curable) gastric cancer [36]. Our study included data from 2004 to 2015, while the SEER database lacks records about D2 lymphadenectomy. Therefore, the role of RT in GC patients without D2 lymph node dissection could not be assessed in this study. Next, several prognostic biomarkers that were not included in the SEER database may also play an important role in identifying the role of RT. For example, HER2 status, microsatellite instability (MSI) status, and expression of programmed death-ligand 1 (PD-L1), all of these biomarkers have been shown to have a significant impact on clinical practice and patient care [11]. However, this effect could not be reduced in the present study. Future studies may pay attention on these biomarkers and identify optimal subgroups in the era of precision medicine. What's more, ethnicity is also an important factor affecting CSS. In contrast, the majority of our study population was white (approximately 70 %). Therefore, our findings may not be applicable to other ethnic groups. Finally, because this was a retrospective study, there may have been selection bias. These questions need to be addressed by further prospective randomized controlled trials, as well as patients of different ethnicities or multicenter studies.

5. Conclusion

A retrospective analysis of the SEER big data showed that the benefit of adjuvant radiotherapy was greater than that of neoadjuvant radiotherapy or no radiotherapy in patients with $T_{1\text{-}2}N^{+}$, T_3N^{-}, and T_3N^{+} locally advanced gastric cancer. The results of this study are not consistent with the recommendations of the NCCN and ESMO guidelines. Therefore, the optimal timing of radiotherapy in this population still needs to be further explored. Compared with randomized controlled trials, evidence from observational studies can better reflect the real results in clinical practice, so more evidence from the real world is needed.

Declarations

Availability of data and material: The datasets for this study can be obtained from the corresponding author upon any reasonable request.

Ethics approval: As this study is a retrospective analysis of public dataset, ethical approval for this study was not required.

CRediT authorship contribution statement

Guangrong Yang: Formal analysis, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Qiao Yang:** Data curation, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Lin Cui:** Data curation, Formal analysis, Methodology, Resources, Writing – original draft, Writing – review & editing. **Qiang Dong:** Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Zhu Meng:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Changqing Yang:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Jianguo Sun:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25461.

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