Association of survival with adjuvant chemotherapy in patients with stage IB gastric cancer: a multicentre, observational, cohort study

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Summary

Background Recurrence following radical resection in patients with stage IB gastric cancer (GC) is not uncommon. However, whether postoperative adjuvant chemotherapy could reduce the risk of recurrence in stage IB GC remains contentious.

Methods We collected data on 2110 consecutive patients with pathologic stage IB (T1N1M0 or T2N0M0) GC who were admitted to 8 hospitals in China from 2009 to 2018. The survival of patients who received adjuvant chemotherapy was compared with that of postoperative observation patients using propensity score matching (PSM). Two survival prediction models were constructed to estimate the predicted net survival gain attributable to adjuvant chemotherapy.

Findings Of the 2110 patients, 1344 received adjuvant chemotherapy and 766 received postoperative observation. Following the 1-to-1 matching, PSM yielded 637 matched pairs. Among matched pairs, adjuvant chemotherapy was not associated with improved survival compared with postoperative observation (OS: hazard ratio [HR], 0.72; 95% CI, 0.52–1.00; DFS: HR, 0.91; 95% CI, 0.64–1.29). Interestingly, in the subgroup analysis, reduced mortality after adjuvant chemotherapy was observed in the subgroups with elevated serum CA19-9 (HR, 0.22; 95% CI, 0.08–0.57; $P = 0.001$ for multiplicative interaction), positive lymphovascular invasion (HR, 0.32; 95% CI, 0.17–0.62; $P < 0.001$

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for multiplicative interaction), or positive lymph nodes (HR, 0.17; 95% CI, 0.07–0.38; $P < 0.001$ for multiplicative interaction). The survival prediction models mainly based on variables associated with chemotherapy benefits in the subgroup analysis demonstrated good calibration and discrimination, with relatively high C-indexes. The C-indexes for OS were 0.74 for patients treated with adjuvant chemotherapy and 0.70 for patients treated with postoperative observation. Two nomograms were built from the models that can calculate individualized estimates of expected net survival gain attributable to adjuvant chemotherapy.

Interpretation In this cohort study, pathologic stage IB alone was not associated with survival benefits from adjuvant chemotherapy compared with postoperative observation in patients with early-stage GC. High-risk clinicopathologic features should be considered simultaneously when evaluating patients with stage IB GC for adjuvant chemotherapy.

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Keywords: Adjuvant chemotherapy; Stage IB; Gastric cancer; CA19-9; Lymphovascular invasion

Research in context

Evidence before this study

Although many randomized clinical trials have assessed the role of adjuvant chemotherapy in patients with resected stage II to III gastric cancer (GC), the benefits from adjuvant therapy for those with stage IB GC still lack evidence. We searched PubMed using the terms ("stage I" OR "stage IB" OR "T2N0" OR "T1N1") AND "gastric cancer" AND ("adjuvant chemotherapy" OR "adjuvant chemoradiotherapy") from database inception up to September 30, 2023, with no language restrictions. Only 12 retrospective studies about the association between adjuvant therapy and survival in patients with stage IB GC were published. However, only four multicentre studies were identified and all of them extracted the data from the same US SEER database. The remaining 8 studies had various limitations, including a small sample size, single-center design, and no construction of survival prediction model. Importantly, these studies have drawn controversial conclusions.

Added value of this study

Our study is the largest multicentre to present the most authoritative and comprehensive data evaluating the effect of adjuvant chemotherapy on survival in stage IB GC. This study is also the first to cover the detailed recurrence patterns and treatment of patients with stage IB GC in multiple hospitals, and construct models to predict the individualized net survival benefit of adjuvant chemotherapy. This study adds the Asian population to international data on adjuvant chemotherapy benefits in patients with early GC. Our results show that pathologic stage IB alone was not associated with survival benefit from adjuvant chemotherapy compared with postoperative observation in patients with early GC. In the subgroup analysis, only patients with high-risk clinicopathologic features, including positive lymphovascular invasion, elevated serum CA19-9, and positive lymph nodes, showed a significant survival benefit from adjuvant chemotherapy. Two nomograms were built to estimate the net survival gain attributable to the receipt of adjuvant chemotherapy for patients with stage IB GC. The models predict the survival benefits very well.

Implications of all the available evidence

The findings suggest that high-risk clinicopathologic factors should be simultaneously considered when evaluating patients with stage IB GC for adjuvant chemotherapy.

Introduction

Gastric cancer (GC) is one of the major causes of cancer deaths worldwide, especially in Eastern and Central Asia.[1] With the prevalence of gastroscopes for screening and improvement in diagnostic capabilities, more patients are being detected at early stages.[2] In Japan and Korea, stage I GC accounts for 50% of the total number of GC operations.[3,4] In the 8th edition of the TNM classification for GC according to the American Joint Committee on Cancer (AJCC) system, stage I has been classified into stages IA and IB, of which stage IB includes pT1N1M0 and pT2N0M0.[5] In cases of stage IB GC, the 5-year survival rate has been reported to be 65–90%.[5–8] The cumulative probability of recurrence for stage IB GC ranges from 7.5 to 21.3% over the 5 years of follow-up after operation,[6,7,9] some of which even recur very shortly after surgery, suggesting that some stage IB GC patients have a high recurrence rate and poor prognosis. The addition of adjuvant chemotherapy after radical surgical resection has demonstrated a survival benefit in patients with stage II to III GC.[10,11] Therefore, effective postoperative adjuvant chemotherapy may be necessary for some high-risk patients with stage IB GC to minimize the risk of recurrence after surgery.

To date, no randomized controlled trials have attempted to define a role for adjuvant therapy after surgery for stage IB GC. Unfortunately, several retrospective studies with small sample sizes have drawn controversial conclusions.[12–14] Studies from Korea showed no benefits from adjuvant therapy in patients with pT1N1 GC after radical operation.[9,13] Nevertheless, Caitlin et al. showed that adjuvant therapy was independently associated with improved survival in patients with pT1N1 GC in a heterogeneous western population.[14] For pT2N0 GC from the Surveillance, Epidemiology, and End Results (SEER) database of the US National Cancer Institute, patients with pT2N0M0 GC may not benefit from adjuvant therapy.[8] Due to the lack of direct evidence, the Japanese guidelines recommend observation following resection for stage IB patients.[15] In contrast, the American National Comprehensive Cancer Network (NCCN) guidelines recommend adjuvant therapy for high-risk stage IB patients, such as those with metastatic lymph nodes, age below 50 years, or poorly differentiated tumors.[16] However, this recommendation was mainly based on a single-center retrospective study of 233 patients with T2N0 GC. Consequently, other important risk factors might have been missed. Taken together, clinicians currently have little evidence to rely on when determining whether adjuvant chemotherapy will be beneficial to their stage IB patients.

The Multidisciplinary Alliance of Gastric Integrative Studies (MAGIS) cohort is a comprehensive data resource that includes 15 well-known centers across China.[17,18] Using data from the MAGIS cohort, we assessed the impact of adjuvant chemotherapy on the survival of patients with stage IB GC and defined the type of patients who would benefit from chemotherapy. To facilitate decision-making for an individual stage IB GC patient, we also developed a user-friendly prediction model that can be used to estimate the net survival gain attributable to the receipt of adjuvant chemotherapy.

Methods

Database and patient population

We retrospectively extracted the data from the prospective MAGIS database of consecutive patients with GC who were admitted for radical gastrectomy from January 2009 to December 2018. In total, the MAGIS database was from 15 hospitals across China. To reduce the inherent bias of a retrospective study, only 8 large tertiary care hospitals with prospective follow-up of all patients with GC who underwent resection surgery were eligible as sources for the current study. The study cutoff date was June 30, 2022, which is the date of the last update of the MAGIS database on the follow-up time.

All these patients satisfied the following inclusion criteria: gastric adenocarcinoma; older than 18 years; pathologic stage T2N0M0 or T1N1M0 (8th AJCC TNM staging manual); curative resection (R0); no prior history of malignant tumors or synchronous other sites of primary malignancy; no history of gastrectomy; no neoadjuvant therapy; survival time over 30 days after surgery; and complete treatment information. After excluding 315 ineligible cases, we included 2110 consecutive GC patients in this study (Fig. 1). The Ethical Committee of Xijing Hospital approved this multicentre study (KY20182088-F-1) and waived the need to obtain patient informed consent. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Data elements

The following high-risk clinicopathological features were selected by the NCCN guidelines and previous studies[14,19,20]: age, tumor differentiation, lymphovascular invasion (LVI), nerve invasion, lymph node harvesting, tumor size, preoperative carcinoembryonic antigen (CEA), and carbohydrate antigen 19-9 (CA19-9). Other independent variables included the following: sex, body mass index (BMI), Charlson Comorbidity score, primary tumor location, type of surgical resection (proximal, distal, or total), operation (open or laparoscopy), extent of lymphadenectomy (D1+ or D2), and length of stay after surgery.

Patients underwent adjuvant chemotherapy or observation based upon a decision made by the patient and the medical oncologist. Among 1344 patients who received adjuvant chemotherapy, 504 (37.5%) received single-agent S1, 241 (17.9%) received S-1 and oxaliplatin (SOX), 157 (11.7%) received capecitabine and oxaliplatin (CapOx), 227 (16.9%) received fluorouracil, folinic acid, and oxaliplatin (FOLFOX), 83 (6.2%) received 5-fluorouracil and paclitaxel/docetaxel, and the details of the agents were not available for 132 patients (9.8%) (Supplementary Table S1). Effective chemotherapy was defined as the receipt of at least one cycle of adjuvant chemotherapy.

Follow-up was mainly carried out by telephone or patient visit. Death was confirmed using data from the Civil Registration System. The primary outcome included overall survival (OS), defined as the time from the day of GC operation until death from any cause, censoring those alive at the last follow-up. The secondary outcome included disease-free survival (DFS), defined as the time from the date of primary surgery until the first evidence of disease recurrence or death from GC, censoring patients alive and disease free at the last follow-up. The third outcome included cancer-specific survival (CSS), defined as the time from surgery to death due to GC, censoring patients alive or causes of deaths other than GC at the last follow-up.

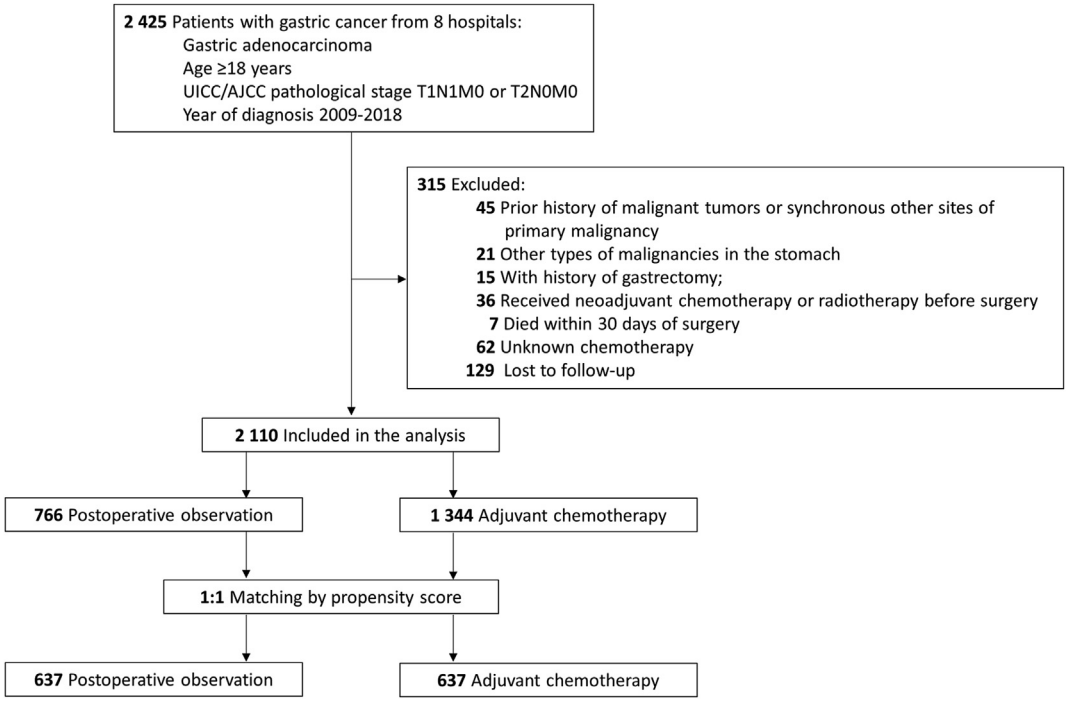

Fig. 1: CONSORT diagram.

Statistical analysis

Statistical analysis was performed from July 1, 2022, to May 30, 2023. Bivariate analyses were performed using the χ^2 test (or Fisher's exact test for those with small sample sizes) for categorical variables and Student's t test (or Kruskal–Wallis test for those who do not meet the assumptions of normal distribution) for continuous variables. All comparisons were statistically significant for two-tailed $P < 0.05$. All statistical analyses were performed using R version 4.1.1.

Based on previous studies, the estimated 5-year OS rate for those receiving postoperative observation is 80%, and the estimated 5-year OS rate for those receiving adjuvant chemotherapy is 90%. It is anticipated that the proportion of subjects that are lost during follow-up is 10%. On the basis of these assumptions, samples of 213 subjects in per arm achieve 90% power to detect a hazard ratio of 0.472 when the significance level (alpha) is 0.15 using a two-sided test.

We used random forest imputation (missForest package version 1.5) to deal with the missing data. All variables with missing data were included as its predictors. Missing data on our study variables ranged from 0% to 15%, including tumor size (2.2% missing), tumor differentiation (1.1%), LVI (3.3%), BMI (15.3%), CEA 237 (11.2%), CA19-9 279 (13.2%), neural invasion 224 (10.6%), and number of lymph nodes examined 14 (0.7%). Supplementary Table S2 shows the variables before and after imputation. We used the completed data for the following analysis.

Analysis of prognostic relevance of chemotherapy

To explore the relationship between adjuvant chemotherapy status and the clinical outcome of GC, univariate and multivariable analyses were performed based on the Cox proportional hazards model. Variables were included in the multivariable analysis, including age, positive lymph node number (0, 1, 2), type of gastrectomy (proximal, distal, total), primary tumor location (proximal, body, antrum), and TNM stage (T2N0, T1N1). These variables produced over 10% change in the regression coefficient of adjuvant chemotherapy status after they were introduced into the basic model and removed from the full model. Three models of Cox proportional hazards analyses were performed to determine the hazard ratio (HR) for clinical outcome: (i) non-adjusted model; (ii) Model I adjusted for age; and (iii) Model II adjusted for age, positive lymph node number, type of gastrectomy, primary tumor location, and TNM stage.

We applied two methods to evaluate the robustness of HR estimates in a sensitivity analysis. We used the R package "MatchIt" version 4.5.5 to perform propensity score matching (PSM) to eliminate potential confounding factors. One-to-one PSM between the adjuvant chemotherapy group and the no adjuvant chemotherapy group was performed via the greedy-matching algorithm, with a caliper width equal to 0.01 of the standard deviation of the logit of PSM. Propensity score was estimated by the significant variables in Table 1, including age (continuous), sex, lymphovascular invasion (no, yes),

Characteristic	Patients, No. (%)		P value
	Observation (n = 766)	Adjuvant chemotherapy (n = 1344)	
Age, mean (SD), y	61.3 ± 10.6	56.7 ± 10.1	<0.001
Age category, year			
<50	102 (13.3)	302 (22.5)	
≥50	664 (86.7)	1042 (77.5)	
BMI, mean (SD), kg/m^2	23.6 ± 3.3	23.6 ± 3.2	0.636
Tumor size, mean (SD), cm	3.0 ± 1.4	3.1 ± 1.6	0.329
Sex			<0.001
Male	635 (82.9)	1022 (76.0)	
Female	131 (17.1)	322 (24.0)	
CEA, ng/ml			0.963
<5	685 (89.4)	1201 (89.4)	
≥5	81 (10.6)	143 (10.6)	
CA19–9, U/ml			0.944
<37	734 (95.8)	1287 (95.8)	
≥37	32 (4.2)	57 (4.2)	
Lymph nodes examined			0.102
≥16	565 (73.8)	1034 (76.9)	
<16	201 (26.2)	310 (23.1)	
Lymphovascular invasion			<0.001
No	666 (86.9)	1047 (77.9)	
Yes	100 (13.1)	297 (22.1)	
Nerve invasion			<0.001
No	655 (85.5)	1000 (74.4)	
Yes	111 (14.5)	344 (25.6)	
Lymph nodes (+) number			<0.001
0	696 (90.9)	985 (73.3)	
1	50 (6.5)	258 (19.2)	
2	20 (2.6)	101 (7.5)	
Differentiation			0.012
High	91 (11.9)	119 (8.9)	
Middle	447 (58.4)	755 (56.2)	
Low/Undifferentiated	228 (29.8)	470 (35.0)	
Operation			0.684
Open	558 (72.8)	990 (73.7)	
Laparoscopy	208 (27.2)	354 (26.3)	
Type of gastrectomy			<0.001
Proximal	269 (35.1)	236 (17.6)	
Distal	386 (50.4)	877 (65.3)	
Total	111 (14.5)	231 (17.2)	
Primary tumor location			<0.001
Proximal	269 (35.1)	296 (22.0)	
Body	138 (18.0)	258 (19.2)	
Antrum	359 (46.9)	790 (58.8)	
Extent of lymphadenectomy			<0.001
D1+	183 (23.9)	235 (17.5)	
D2	583 (76.1)	1109 (82.5)	
TNM Stage (AJCC 8th)			<0.001
T2N0	696 (90.9)	985 (73.3)	
T1N1	70 (9.1)	359 (26.7)	
Charlson score			0.009
0	609 (79.5)	1129 (84.0)	
≥1	157 (20.5)	215 (16.0)	
Inhospital time (week)			<0.001
<2	689 (89.9)	1269 (94.4)	
≥2	77 (10.1)	75 (5.6)	

AJCC, American Joint Committee on Cancer; CA19-9, cancer antigen 19-9; CEA, carcinoembryonic antigen; No., number; SD, standard deviation.

Table 1: **Baseline characteristics of patients receiving adjuvant chemotherapy vs observation only for patients with stage IB gastric cancer in the original data sets.**

nerve invasion (no, yes), lymph nodes (+) number (0, 1, 2), differentiation (high, middle, low/undifferentiated), type of gastrectomy (proximal, distal, total), primary tumor location (proximal, body, antrum), extent of lymphadenectomy (D1+, D2), TNM stage (T2N0, T1N1), Charlson score (0, ≥1), and inhospital time (<2 weeks, ≥2 weeks). Supplementary Table S3 showed the baseline characteristics of patients receiving adjuvant chemotherapy vs observation in the matched data sets. Besides, the distribution of propensity-matching adjuvant chemotherapy after matching was listed in Supplementary Fig. S1. Then subgroup analyses were performed to search for potential heterogeneity sources, including age, sex, CEA, CA19-9, lymph nodes harvesting, LVI, neural invasion, differentiation, operation, extent of lymphadenectomy, TNM Stage, and Charlson score, with tests for multiplicative interaction by the Cox regression model adjusted for propensity score. The relative excess risk due to interaction (RERI) was calculated to reflect additive interactions.

Development and validation of the prediction model

Multivariable regression analysis was conducted using Cox proportional hazards modeling, which formed the basis for the survival prediction model. Covariates were included in the multivariable analyses via the stepwise regression method. Covariates were included in the multivariable analyses via the stepwise regression method based on the principle of minimum Akaike Information Criterion (AIC), including age, sex, BMI, LVI, location, CEA, and TNM stage (T1N1, T2N0). Combined with clinical significance, CA19-9 was also included in the final prediction model. The prediction model was implemented into nomograms to enable use on plain paper and implementation as a calculation tool. The survival prediction model was developed based on patients with or without adjuvant chemotherapy, respectively. It was validated by measuring both

discrimination and calibration. Both discrimination and calibration were evaluated on the original study cohort using bootstrapping with 1000 resamples. Discrimination was evaluated using the concordance index (C-index). Calibration was evaluated with a calibration curve.

Clinical use

Net benefit analysis of adjuvant chemotherapy was performed to determine the clinical usefulness of the nomograms by quantifying the disparity in predicted 5-year OS between the two nomograms.

Role of the funding source

The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.

Results

Patient characteristics

The baseline clinicopathological characteristics of the 2110 patients in the study are summarized in Table 1. The median follow-up time after GC surgery was 6.20 years (interquartile range: 4.68–8.55). Among 2110 patients, 170 patients (8.1%) experienced recurrence, 221 patients (10.5%) died, and 270 patients (12.8%) experienced recurrence or death (Table 2 lists a detailed distribution of recurrence). With respect to OS, 614 (29.1%) patients were censored before 5 years; 92.0% were still alive (95% CI, 91.4%–92.7%) at that time. Summarized events for OS, DFS, and CSS are presented in Supplementary Table S4.

Of the 2110 patients, 1344 received adjuvant chemotherapy, and 766 received postoperative observation (surgery only). As might be expected by indication bias, patients receiving adjuvant chemotherapy were younger than those receiving surgery only (mean age, 56.7 ± 10.1 years vs 61.3 ± 10.6 years; $P < 0.001$), more likely to have LVI (297 [22.1%] vs 100 [13.1%]; $P < 0.001$), nerve invasion (344 [25.6%] vs 111 [14.5%]; $P < 0.001$), pT1N1 (359 [26.7%] vs 70 [9.1%]; $P < 0.001$), low/undifferentiated histologic features (470 [35.0%] vs 228 [29.8%]; $P = 0.012$), and shorter inpatient length of stay (>2 weeks: 75 [5.6%] vs 77 [10.1%]; $P < 0.001$) (Table 1).

Pathologic stage/recurrence patterns	No. of recurrences (T1N1/T2N0)	Recurrences in each postoperative year, No.							
		1 y	2 y	3 y	4 y	5 y	6 y	7 y	>7 y
Chemotherapy	107	22	24	18	16	8	8	3	8
Locoregional	9/15	1/2	2/2	1/6	2/1	0/0	1/0	1/0	1/4
Hematogenous	3/34	1/8	0/10	0/5	1/6	0/1	0/3	0/0	1/1
Peritoneal	1/12	0/1	0/2	0/3	1/3	0/2	0/0	0/1	0/0
LNM	0/13	0/6	0/3	0/0	0/1	0/1	0/1	0/1	0/0
Mixed	5/15	1/2	0/5	1/2	0/1	1/3	2/1	0/0	0/1
No chemotherapy	63	19	14	7	10	6	3	2	2
Locoregional	0/12	0/3	0/4	0/0	0/0	0/3	0/0	0/0	0/2
Hematogenous	4/25	2/7	1/4	0/3	1/5	0/2	0/3	0/1	0/0
Peritoneal	1/9	0/3	1/3	0/1	0/1	0/1	0/0	0/0	0/0
LNM	1/7	0/2	1/0	0/2	0/2	0/0	0/0	0/1	0/0
Mixed	1/3	1/1	0/0	0/1	0/1	0/0	0/0	0/0	0/0

Abbreviations: LNM, lymph node metastasis; No., number.

Table 2: **Recurrence patterns after radical gastrectomy.**

Association of chemotherapy with survival based on clinicopathological features

In the original (unmatched) data, the addition of adjuvant chemotherapy was associated with a higher rate of OS and CSS compared with receiving surgery only (HR, 0.55; 95% CI, 0.42–0.72; $P < 0.001$ and HR, 0.67; 95% CI, 0.49–0.93; $P = 0.015$) (Table 3, Fig. 2A and Supplementary Fig. S2A). However, a comparative analysis of DFS showed no statistical significance (HR, 0.79; 95% CI, 0.60–1.05; $P = 0.102$) (Table 3, Fig. 2B). Compared with the surgery only group, the HRs for OS and DFS in the adjuvant chemotherapy group were 0.83 (95% CI, 0.62–1.11; $P = 0.210$) and 1.05 (95% CI, 0.77–1.41; $P = 0.761$) by Cox regression adjusted for the other confounding variables (Table 3). Adjuvant chemotherapy was not an independent predictor of mortality.

Following the 1-to-1 matching by propensity score, PSM yielded 637 matched pairs that were well-balanced in baseline clinicopathologic characteristics. Adjuvant chemotherapy was not significantly associated with improved OS (HR, 0.72; 95% CI, 0.52–1.00; $P = 0.052$), DFS (HR, 0.91; 95% CI, 0.64–1.29; $P = 0.601$) or CSS (HR, 0.85; 95% CI, 0.57–1.26; $P = 0.406$) compared with surgery alone in these patients (Table 3, Fig. 2C and D, and Supplementary Fig. S2B).

In the subgroup analyses of OS (Table 4), a strong multiplicative interaction was observed between treatment and CA19-9 (<37 vs ≥ 37 U/ml, $P = 0.001$ for multiplicative interaction), LVI (no vs yes, $P < 0.001$ for multiplicative interaction), and TNM stage (T2N0 vs T1N1, $P < 0.001$ for multiplicative interaction). The patients who received adjuvant chemotherapy showed significantly better OS rates than those who did not in the subgroups with elevated serum CA19-9 (HR, 0.22; 95% CI, 0.08–0.57; $P = 0.002$), positive LVI (HR, 0.32; 95% CI, 0.17–0.62; $P < 0.001$), and T1N1 (HR, 0.17; 95% CI, 0.07–0.38; $P < 0.001$); no difference was observed in the subgroups with normal serum CA19-9 (HR, 0.90; 95% CI, 0.66–1.22; $P = 0.542$), negative LVI (HR, 0.98; 95% CI, 0.71–1.35; $P = 0.959$), or those with negative lymph nodes (T2N0) (HR, 0.95; 95% CI, 0.71–1.28; $P = 0.792$). Additionally, no significant differences in treatment effect were seen between groups in either population when stratified by sex, age, CEA, nerve invasion, differentiation, lymph node harvesting,

Before PSM	Event/N	Non-adjusted		Model I		Model II	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
OS	221/2110	0.55 (0.42, 0.72)	<0.001	0.72 (0.55, 0.95)	0.019	0.83 (0.62, 1.11)	0.210
DFS[a]	197/2100	0.79 (0.60, 1.05)	0.102	0.91 (0.68, 1.22)	0.538	1.05 (0.77, 1.41)	0.761
After PSM							
OS	145/1274	0.72 (0.52, 1.00)	0.052	–		–	
DFS[a]	125/1268	0.91 (0.64, 1.29)	0.601	–		–	

Model I adjusted for: age. Model II adjusted for: age, positive lymph nodes number (0, 1, 2), type of gastrectomy (proximal, distal, total), primary tumor location (proximal, body, antrum), and TNM stage (T2N0, T1N1). These variables produced over 10% change in the regression coefficient of adjuvant chemotherapy status after they were introduced into the basic model and removed from the full model. CI: confidence interval; DFS, disease-free survival; HR, hazard ratio; OS, Overall survival; PSM, propensity score matching. [a]Because 10 patients died at home without medical examination, and it was unclear whether they suffered from gastric cancer recurrence, they were excluded from the DFS analysis. After PSM, 6 patients without causes of death were excluded from the DFS analysis.

Table 3: **Univariable and multivariable analysis of overall survival and disease-free survival.**

operation, extent of lymphadenectomy, and Charlson score (all $P \geq 0.10$ for multiplicative interaction). The results of additive interactions were consistent with those of multiplicative interactions.

Application of number of risk factors in predicting benefits from adjuvant chemotherapy

To examine the cumulative predictive value of recurrence or death and select the relatively high-risk patients as candidates for adjuvant chemotherapy, LVI, elevated CA19-9, and lymph node metastasis were used as three risk predictors. We divided all patients into three groups according to the number of positive risk predictors: none positive (n = 1,373, 65.1%), one positive (n = 564, 26.7%), and more than one positive (n = 173, 8.2%). In Fig. 3, adjuvant chemotherapy was not significantly associated with improved OS compared with surgery only in the none-positive (HR, 0.84; 95% CI, 0.61–1.16; $P = 0.283$). In contrast, adjuvant chemotherapy was significantly associated with improved OS in both one positive (HR, 0.31; 95% CI, 0.18–0.52; $P < 0.001$) and more than one positive group (HR, 0.05; 95% CI,

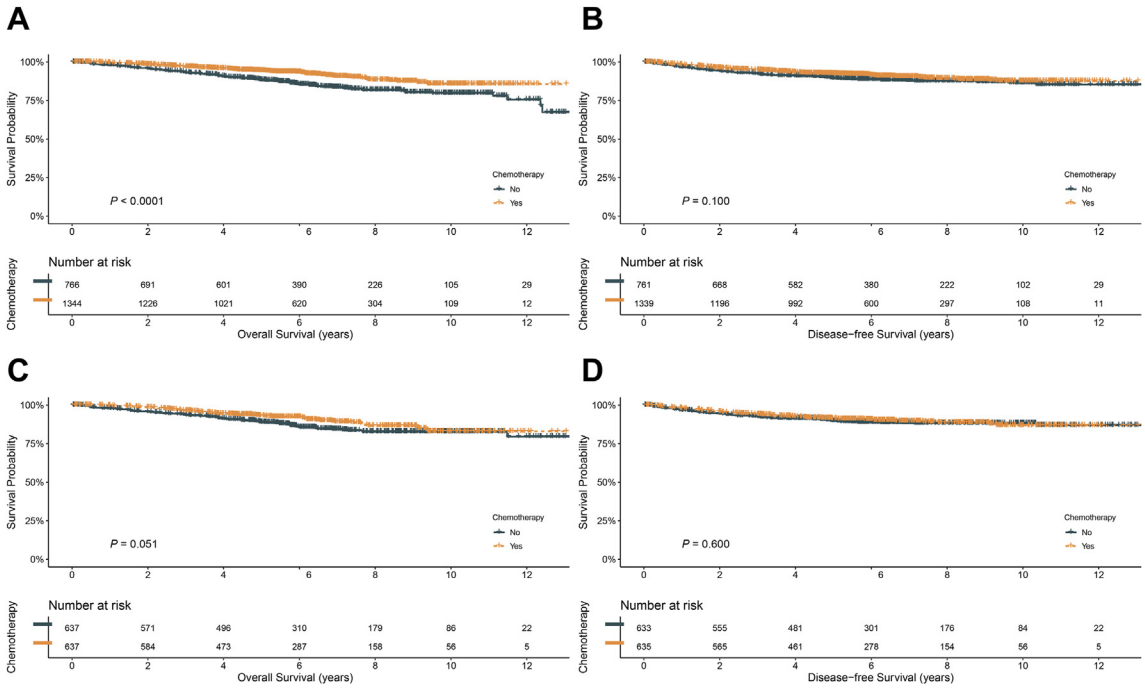

Fig. 2: Kaplan–Meier curve for overall survival and disease-free survival between patients in the adjuvant chemotherapy group and patients in the observation-only group. Original (unmatched) data (A, B), and matched data (C, D). Because 10 patients died at home without medical examination, and it was unclear whether they suffered from gastric cancer recurrence, they were excluded from the disease-free survival analysis. In matched data, 6 patients without causes of death were excluded from the disease-free survival analysis.

Subgroups	Death events	No. of patients (%)	Adjusted HR (95% CI)	*P* value	P[a] for interaction	RERI (95% CI)	P[b] for interaction
Sex					0.540	−0.02 (−0.47 to 0.44)	0.944
Male	191	1657	0.80 (0.59, 1.08)	0.177			
Female	30	453	0.78 (0.34, 1.80)	0.566			
Age, years					0.282	0.33 (−0.04 to 0.70)	0.079
≥50	198	1706	0.79 (0.58, 1.07)	0.156			
<50	23	404	1.02 (0.39, 2.67)	0.979			
CEA					0.237	−1.22 (−2.66 to 0.21)	0.095
<5	171	1886	0.84 (0.61, 1.17)	0.356			
≥5	50	224	0.55 (0.30, 1.02)	0.058			
CA19-9					0.001	−3.31 (−5.89 to −0.73)	0.012
<37	198	2021	0.90 (0.66, 1.22)	0.542			
≥37	23	89	0.22 (0.08, 0.57)	0.002			
Lymph nodes harvesting					0.728	−0.36 (−1.06 to 0.34)	0.313
≥16	138	1599	0.78 (0.54, 1.12)	0.207			
<16	83	511	0.76 (0.48, 1.22)	0.273			
LVI					<0.001	−1.24 (−2.24 to −0.25)	0.014
No	180	1713	0.98 (0.71, 1.35)	0.959			
Yes	41	397	0.32 (0.17, 0.62)	<0.001			
Nerve invasion					0.354	−0.21 (−0.88 to 0.45)	0.529
No	179	1655	0.83 (0.60, 1.14)	0.262			
Yes	42	455	0.70 (0.36, 1.37)	0.333			
Differentiation					0.446	0.22 (−0.16 to 0.61)	0.255
High/middle	150	1412	0.75 (0.52, 1.06)	0.101			
Low/undifferentiated	71	698	0.96 (0.58, 1.59)	0.867			
Operation					0.566	0.03 (−0.42 to 0.49)	0.897
Open	168	1548	0.85 (0.61, 1.18)	0.360			
Laparoscopy	53	562	0.69 (0.39, 1.22)	0.222			
Extent of lymphadenectomy					0.177	−0.28 (−0.89 to 0.34)	0.374
D1+	55	418	1.03 (0.58, 1.85)	0.891			
D2	166	1692	0.75 (0.54, 1.04)	0.109			
TNM stage					<0.001	−1.16 (−2.14 to −0.17)	0.021
T2N0	196	1681	0.95 (0.71, 1.28)	0.792			
T1N1	25	429	0.17 (0.07, 0.38)	<0.001			
Charlson score					0.669	−0.35 (−1.02 to 0.31)	0.302
0	170	1738	0.86 (0.62, 1.19)	0.398			
≥1	51	372	0.60 (0.32, 1.13)	0.126			

CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; CI: confidence interval; HR, hazard ratio; LVI, lymphovascular invasion; RERI, relative excess risk due to interaction. [a]*P* for interaction was tested on multiplicative scale. [b]*P* for interaction was tested on additive scale.

Table 4: **Impact of adjuvant chemotherapy on overall survival in patient subgroups.**

0.01–0.16; $P < 0.001$). After adjusting for propensity score, HR of death was 1.17 (95% CI, 0.83–1.64; $P = 0.378$), 0.47 (95% CI, 0.27–0.83; $P = 0.009$), and 0.07 (95% CI, 0.02–0.27; $P < 0.001$) in the none positive, one positive, and more than one positive group, respectively.

To compare the efficacy of the single agent therapy with the multiagent combination therapy for patients with at least one risk factor, the patients were divided into the no chemotherapy group, the single agent therapy group, and the multiagent combination therapy group (SOX, CapOx, and FOLFOX). Compared with the no chemotherapy group, the HRs for OS and CSS in the single agent therapy group were 0.19 (95% CI, 0.10–0.38; $P < 0.001$) and 0.23 (95% CI, 0.11–0.51; $P < 0.001$), respectively; the HRs for OS and CSS in the multiagent combination therapy group were 0.18 (95% CI, 0.10–0.34; $P < 0.001$) and 0.26 (95% CI, 0.13–0.51; $P < 0.001$), respectively (Supplementary Fig. S3). The efficacy outcomes associated with single agent therapy were similar to those achieved with multi-agent combination therapy.

Development of the prediction model to guide chemotherapy decision making

To estimate individualized risk, multivariable Cox regressions were conducted separately for patients who

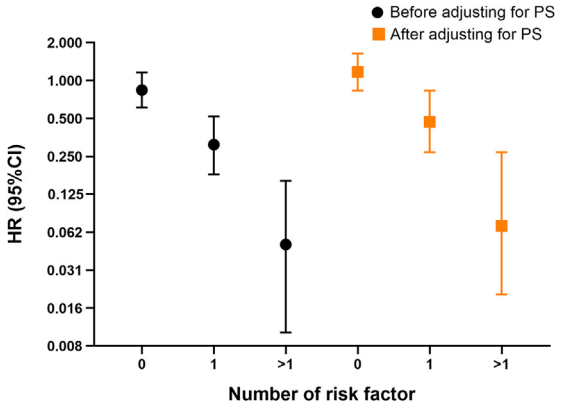

Fig. 3: Mortality hazard ratios according to the number of baseline risk features. CI: confidence interval; HR, hazard ratio; PS, propensity score.

underwent surgery only and adjuvant chemotherapy. The β coefficients from the Cox multivariable models were used to construct two predictive nomograms. To calculate the net survival benefit from adjuvant chemotherapy, the 2 nomograms were used at the same time (Fig. 4A and B). The upper nomogram (Fig. 4A) estimates the predicted OS without adjuvant chemotherapy, and the lower nomogram (Fig. 4B) estimates OS with adjuvant chemotherapy. The expected net survival benefit from the addition of adjuvant chemotherapy is equal to the difference between the two estimates.

Nomogram model performance was internally validated for discrimination and calibration. The C-indexes for OS were 0.74 (95% CI, 0.69–0.78) in the group treated with adjuvant chemotherapy and 0.70 (95% CI, 0.65–0.76) in the group treated with surgery only. The calibration curve showed good agreement between the predicted and observed clinical outcomes (Supplementary Fig. S4). In the sensitivity analysis, we repeated the analysis without imputation, which yielded similar results.

Treatment effect prediction

A narrow distribution of predicted gain in 5-year OS by adjuvant chemotherapy was observed in the stage IB GC patients, with a median of 1.0% (IQR –0.8% to 4.9%; Fig. 5). Of the patients, only 24.3% (513/2110) had a predicted gain in 5-year OS by adjuvant chemotherapy of >5%, 38.3% (808/2110) had a predicted gain between 0 and 5% and 37.4% (789/2110) had a predicted treatment effect in favor of postoperative observation (Fig. 5).

Discussion

Our objective was to evaluate the association between adjuvant chemotherapy and survival in patients with stage IB GC. We found that the patients with serum CA19-9 ≥37 U/ml, positive LVI, or positive metastatic lymph nodes had improved survival by chemotherapy in this cohort with early-stage disease. Accordingly, in contrast to patients without a CA19-9 of 37 U/ml or higher, positive LVI, or positive metastatic lymph node, patients who fulfilled two or more of these risk factors had an excellent improved survival by chemotherapy; patients who fulfilled only one risk factor still had an improved outcome by chemotherapy. These findings strongly support the hypothesis that adjuvant chemotherapy is effective for selected stage IB GC patients. To facilitate easy application, we developed simple, easily applicable prediction nomograms—mainly based on variables associated with chemotherapy benefits in the subgroup analysis—that predict the degree of individualized benefit of adjuvant chemotherapy in clinical practice.

To date, no randomized trials have been designed to determine the role of adjuvant chemotherapy after radical surgery for stage IB GC, and conflicting results have been reported from several retrospective studies.[9,12–14,20] To date, this is the largest multicentre study designed to evaluate the effect of adjuvant chemotherapy on survival in stage IB GC. A retrospective study involving patients with stage IB GC from the SEER database showed that stage IB alone was not associated with improved survival from adjuvant chemotherapy.[12] However, the study did not examine some potentially important high-risk clinicopathological features, such as preoperative CEA, CA19-9, and LVI, that might also be associated with the efficacy of chemotherapy. Some studies with detailed clinicopathological information have attempted to identify the risk factors for recurrence after gastrectomy for stage IB GC.[20–22] They showed that those with histologically undifferentiated adenocarcinoma, LVI, large tumor diameter, or perineural invasion were at higher risk of recurrence. Unfortunately, the authors did not evaluate whether the risk for recurrence could be reduced with adjuvant chemotherapy in patients with these high-risk factors.

The results of our study suggest that there is a survival benefit associated with adjuvant chemotherapy in patients with node-positive tumors. These findings are consistent with previous studies conducted in European-American populations.[8,14] Nevertheless, two recent retrospective studies in the Korean population showed that patients with pT1N1 GC might not benefit from adjuvant therapy.[9,13] In our study, the 5-year survival for patients with pT1N1 GC who received adjuvant chemotherapy was on par with the 90–95% 5-year DFS expectation reported in the literature for Korean patients with pT1N1 disease.[9,13] In contrast, our patients with pT1N1 GC treated with surgery only showed a much worse prognosis (5-year DFS only 86.4%). East Asian countries, including China, Japan, and South Korea, are the most high-risk areas for GC. Unlike Japan and South Korea, nearly 80% of patients with GC present

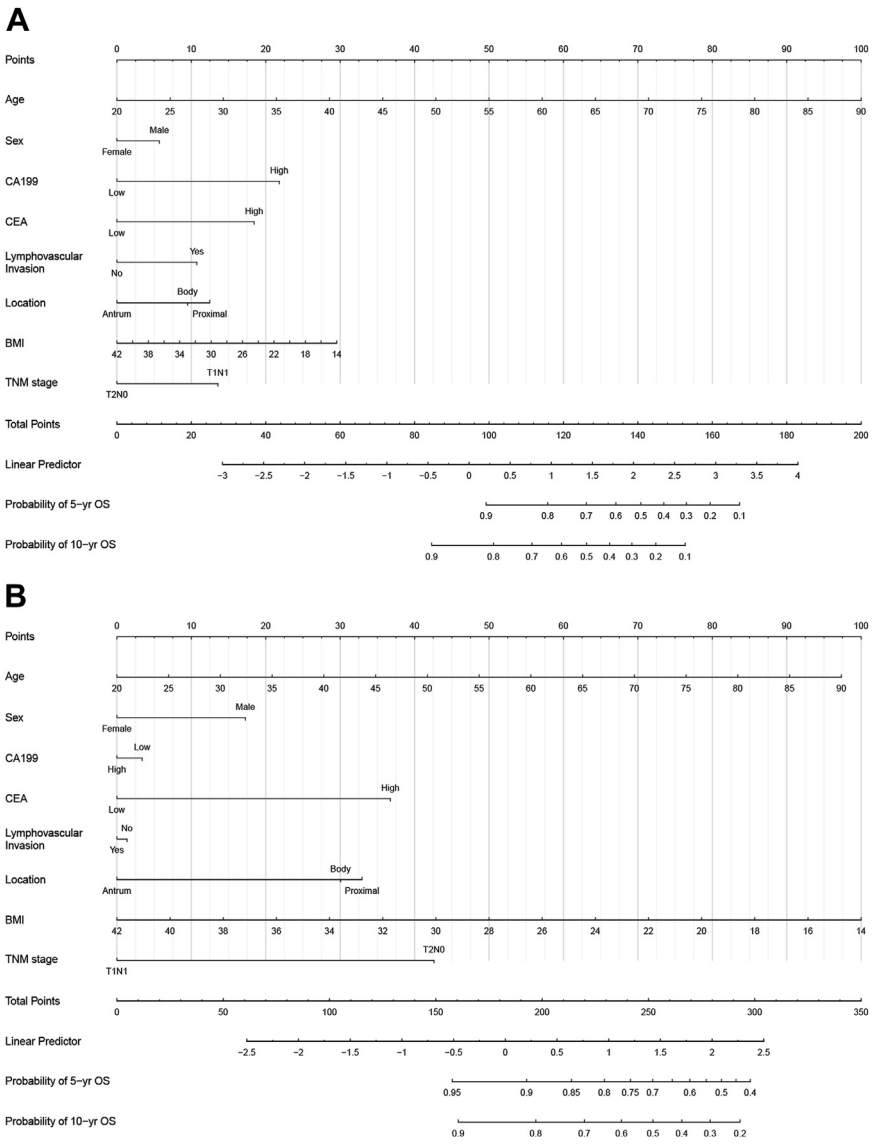

Fig. 4: Nomograms for comparing expected overall survival of patients receiving postoperative observation vs adjuvant chemotherapy. For an individual patient, first use the upper nomogram A to calculate the expected OS with postoperative observation; then use the lower nomogram B to calculate the expected OS with postoperative adjuvant chemotherapy. The difference between the two estimates is the expected net survival gain from adjuvant chemotherapy. BMI, body mass index; CA199, carbohydrate antigen 199; CEA, carcinoembryonic antigen; OS, overall survival; yr, year.

with advanced disease in China.[19] Therefore, heterogeneous study populations and different genetic backgrounds may be responsible for at least some of this apparent difference in adjuvant chemotherapy benefit. Of note, one recent study reported that adjuvant chemotherapy was effective for T2N0 GC patients with less than 15 lymph nodes examined in Western populations.[23] However, the results of this study did not support this finding. In a previous study, the proportion of patients who had less than 15 lymph nodes examined was high (65.4%),[23] which is significantly higher than that in this study. This indicates that potential metastatic lymph nodes were removed as much as possible in this study. Thus, even if lymph node dissection was suboptimal, these patients still did not benefit from adjuvant chemotherapy.

In previous studies, the LVI has been demonstrated to be an important risk factor for recurrence and death after complete surgery in stage IB GC.[21,24,25] However, whether those high-risk patients could benefit from adjuvant therapy was not clear. The present study is the first to confirm this. During the process of metastasis,

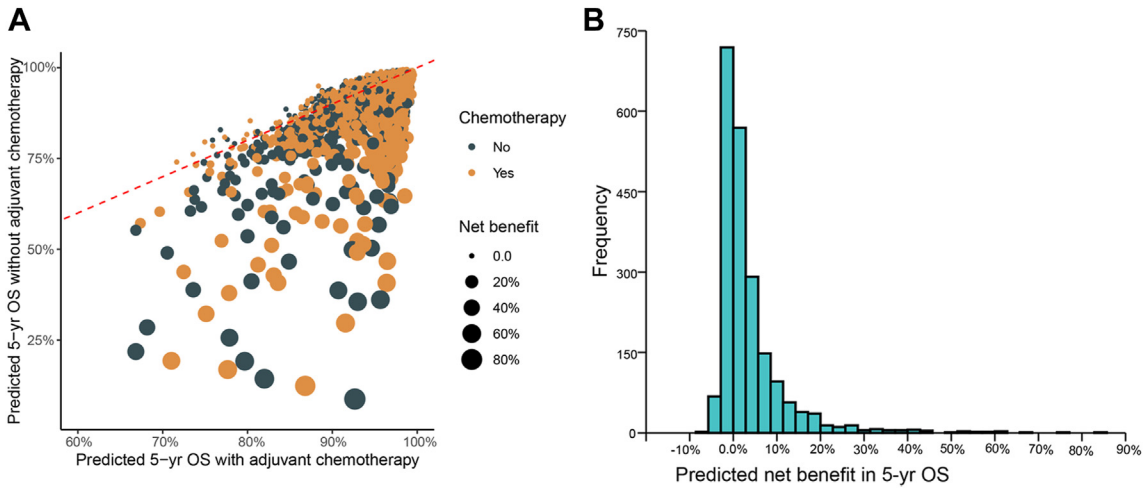

Fig. 5: Distribution of predicted effects of adjuvant chemotherapy vs postoperative observation. (A) Scatter plot with predicted 5-year OS on adjuvant chemotherapy vs predicted 5-year OS on postoperative observation. Orange dots represent patients who received adjuvant chemotherapy and black dots represent patients who received postoperative observation in the original data. Different dot sizes indicate different net benefits. The larger the dot is, the greater the net benefit. (B) Histogram of predicted gain in 5-year OS with adjuvant chemotherapy vs postoperative observation. OS, overall survival; 5-yr, 5-year.

vascular or lymphatic vessels provide a major route by which tumor cells exit the primary sites and become disseminated to regional lymph nodes and distant organs.[26–28] In addition, lymphatic invasion is an independent risk factor for lymph node micrometastasis,[29] which is associated with poor survival in patients with node-negative GC.[30,31] The evidence presented above partly explains why patients with stage IB GC with LVI could benefit from adjuvant chemotherapy.

CEA and CA19-9 are two of the most commonly used tumor markers in GC. It has been confirmed that elevated serum CEA and CA19-9 correlate with a poor clinical outcome.[32,33] Various CEA cutoff point values (4, 5, and 10 ng/ml) were tested, but no significant correlations between CEA and chemotherapy benefit were observed. In contrast to CEA, elevated CA19-9 is not only closely associated with greater tumor burden,[34,35] but also functions as an oncoprotein, promoting aggressive behaviors of cancer cells and hematogenous metastasis.[35,36] Consequently, stage IB GC patients with elevated serum CA19-9 treated with surgery had an overall poor prognosis, while adjuvant chemotherapy can improve the prognosis of these patients.

Clinical prediction nomograms are becoming increasingly popular decision aids for use in guiding postoperative treatment.[37,38] This study makes another important contribution by developing a survival prediction model. The model was able to predict individualized adjuvant chemotherapy benefits and was more predictive than other models. One previous study also established a nomogram to predict OS, but the C-index of the model was only 0.64,[12] lower than that reported in this study (0.70–0.74). The possible reason is that several valuable variables not available within the public SEER database they used were included in our models, including CA19-9 and LVI.

We observed a significant proportion of patients (63.7%) received adjuvant chemotherapy in our study. Indeed, even patients with the same stage of IB, the Chinese patients had a relatively poorer prognosis than the Japanese and Korean patients.[5,39] The previous studies based on Chinese patients show that about 10%–20% of surgical recipients with stage IB GC will suffer from tumor recurrence,[21,39] compared to only 5%–8% in Japanese and Korean patients. This could suggest different underlying molecular biologies across races and ethnicities.[40] Because recurrence risks were relatively high for Chinese stage IB GC, Chinese physicians and patients are cautious in choosing adjuvant therapy. Consistently, the Chinese Society of Clinical Oncology (CSCO) guidelines on GC recommend postoperative adjuvant chemotherapy for patients with high-risk factors, including lymph node metastasis, age below 40 years, poorly differentiated tumors, lymphatic and/or blood vessel invasions, or nerve invasions.[19] These factors may explain the high proportion of patients receiving chemotherapy in this study.

Limitations

Firstly, this is an observational cohort with real-world data. Built-in selection bias and unmeasured confounders were unavoidable,[41] even if we had used PSM to eliminate inherent differences between the two groups. Secondly, because the adjuvant chemotherapy regimens and treatment cycles were inconsistent among patients, we could not conclude which regimen

and how many cycles benefitted patients with stage IB GC. Prospective studies comparing 3 months vs 6 months of adjuvant 5-fluorouracil-based chemotherapy for patients with stage IB GC with high-risk features are warranted. Thirdly, while the overall number of patients included allows for subgroup analysis, the number of patients who suffered GC recurrence or death was low. Therefore, the analysis of HRs as the measure of effect in subgroup analyses is prone to sparse data bias.[42] These findings need to be validated in larger multicentre trials.

Conclusions

These findings suggest that adjuvant chemotherapy provided no survival benefit in unselected patients with stage IB GC. Interestingly, the present study confirmed that LVI, serum CA19-9, and lymph node metastases were predictive of adjuvant chemotherapy benefit with a multicentre design and a large sample of 2110. Since the single agent therapy did not compromise outcomes, oral fluorouracil may be the most appropriate treatment option for patients with at least one risk factor. Meanwhile, we built a survival prediction model that can assist clinicians in quantifying the potential survival benefit from the addition of adjuvant chemotherapy to surgical resection for stage IB GC.

Contributors

Drs X. Gao, Lu, Xi, and Y. Chen had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Wu, Nie, Y. Chen, Xi, Wu, Liang.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: X. Gao, L. Zhao, Lu.
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Statistical analysis: X. Gao, L. Zhao, Lu, Shang.
Obtained funding: Wu, Nie, X. Gao, Deng.
Administrative, technical, or material support: Shang.
Supervision: Xi, Y. Chen, Wu, Nie.

Data sharing statement

The investigators will share de-identified individual participant data following completion of a data use agreement. Data are available after the Article publication from yongznie@fmmu.edu.cn.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101031.

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