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Chemotherapy Use and Survival Among Young and Middle-Aged Patients With Gastric Cancer

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INTRODUCTION: **Treatments for young patients with gastric cancer (GC) remain poorly defined, and their effects on survival are uncertain. We aimed to investigate the receipt of chemotherapy by age category (18–49, 50–64, and 65–85 years) and explore whether age differences in chemotherapy matched survival gains in patients with GC.**

METHODS: **Patients who were histologically diagnosed with GC were included from a Chinese multi-institutional database and the Surveillance, Epidemiology, and End Results database. There were 5,122 and 31,363 patients aged 18–85 years treated between 2000 and 2014, respectively. Overall survival and stage-specific likelihood of receiving chemotherapy were evaluated.**

RESULTS: **Of the 5,122 and 31,363 patients in China and Surveillance, Epidemiology, and End Result data sets, 3,489 (68.1%) and 18,115 (57.8%) were men, respectively. Younger (18–49 years) and middle-aged (50–64 years) patients were more likely to receive chemotherapy compared with older patients (65–85 years) (64.9%, 56.7%, and 45.4% in the 3 groups from the China data set). Among patients treated with surgery alone, a significantly better prognosis was found in younger and middle-aged patients than their older counterparts; however, no significant differences were found in overall survival among age subgroups in patients who received both surgery and chemotherapy, especially in the China data set. The survival benefit from chemotherapy was superior among older patients (all $P < 0.0001$) compared with that among younger and middle-aged patients in stage II and III disease.**

DISCUSSION: **Potential overuse of chemotherapy was found in younger and middle-aged patients with GC, but the addition of chemotherapy did not bring about matched survival improvement, especially in the China data set.**

INTRODUCTION

Gastric cancer (GC) is the third leading cause of tumor-related deaths worldwide and occurs most frequently among the age group of 50–70 years (1–3). Although the incidence and mortality rates of GC among patients aged 50 years and older have decreased about 2% per year worldwide in the past 30 years or longer, the same trend has not been observed for younger adults (1,4). In contrast, the incidence of GC among young adults has steadily increased during the past several decades (5–7). However, currently, the prognosis of younger-onset GC is poorly defined, and survival studies have shown inconsistent results. The results of several studies indicated worse outcome in the young, whereas other studies showed comparable or better outcome relative to patients diagnosed with later-onset disease (5,6,8–10). Because prognosis of young patients with GC is not very clear, it is not easy to give advice on chemotherapy, and the therapeutic regimen for these patients is not well known (6,11–13). Whether younger patients gain survival benefit from chemotherapy remains unknown.

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Received March 27, 2020; accepted September 14, 2020; published online October 14, 2020

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Table 1. Likelihood of receiving postoperative systemic chemotherapy for young (18–49 years) and middle-aged (50–64 years) patients vs older patients (65–85 years) diagnosed with gastric cancer in China and SEER data sets

Patients	China data set				SEER data set			
	Receipt of chemotherapy			OR for receiving chemotherapy (95% CI)[b]	Receipt of chemotherapy			OR for receiving chemotherapy (95% CI)[c]
	Yes (%)	No (%)	P^a		Yes (%)	No (%)	P^a	
All			<0.01				<0.01	
18–49 yr	888 (64.9)	481 (35.1)		2.300 (1.958–2.703)	1,352 (38.1)	2,201 (61.9)		3.054 (2.806–3.324)
50–64 yr	1,357 (56.7)	1,036 (43.3)		1.611 (1.407–1.845)	2,653 (31.0)	5,905 (69.0)		2.178 (2.045–2.320)
65–85 yr	617 (45.4)	743 (54.6)		1 (reference)	3,318 (17.2)	15,934 (82.8)		1 (reference)
Stage I			<0.01				<0.01	
18–49 yr	107 (40.8)	155 (59.2)		2.151 (1.420–3.259)	96 (13.5)	613 (86.5)		2.197 (1.696–2.846)
50–64 yr	159 (35.8)	285 (64.2)		1.862 (1.286–2.697)	251 (11.1)	2,009 (88.9)		1.746 (1.458–2.091)
65–85 yr	53 (23.0)	177 (77.0)		1 (reference)	323 (6.3)	4,779 (93.7)		1 (reference)
Stage II			<0.01				<0.01	
18–49 yr	186 (69.7)	81 (30.3)		2.092 (1.449–3.022)	212 (60.1)	141 (39.9)		4.161 (3.243–5.339)
50–64 yr	331 (61.9)	204 (38.1)		1.431 (1.063–1.927)	506 (49.5)	516 (50.5)		2.700 (2.294–3.117)
65–85 yr	149 (52.3)	136 (47.7)		1 (reference)	652 (25.7)	1,887 (74.3)		1 (reference)
Stage III			<0.01				<0.01	
18–49 yr	476 (72.9)	177 (27.1)		2.753 (2.178–3.479)	314 (64.2)	175 (35.8)		4.075 (3.290–5.048)
50–64 yr	745 (62.9)	440 (37.1)		1.762 (1.459–2.129)	671 (55.4)	541 (44.6)		2.855 (2.467–3.305)
65–85 yr	351 (48.8)	369 (51.3)		1 (reference)	919 (31.0)	2,046 (69.0)		1 (reference)
Stage IV			0.04				<0.01	
18–49 yr	119 (63.6)	68 (36.4)		1.830 (1.128–2.972)	305 (67.0)	150 (33.0)		4.280 (3.334–5.494)
50–64 yr	122 (53.3)	107 (46.7)		1.076 (0.690–1.676)	491 (59.4)	336 (40.6)		2.865 (2.371–3.463)
65–85 yr	64 (51.2)	61 (48.8)		1 (reference)	451 (34.5)	858 (65.5)		1 (reference)

CI, confidence interval; OR, odds ratio; SEER, Surveillance, Epidemiology, and End Result.
[a]Receipt of chemotherapy differs by age group, χ^2 tests.
[b]Model adjusted for sex, tumor size, carcinoembryonic antigen, cancer antigen 19-9, differentiation, and location in China data set.
[c]Model adjusted for sex, race, tumor grade, tumor location, marital status, insurance status, median household income (per $10,000 annual increase), and high school education (per 10% increase) in SEER data set.

Effective treatment improves outcomes of patients with GC (14,15). Surgical resection remains the primary curative option for patients with resectable GC, whereas postoperative chemotherapy is recommended for advanced tumors (14,16–19). Among patients with stage II and stage III disease, adjuvant chemotherapy is recommended as the routine treatment after surgery; however, not every patient could benefit from chemotherapy, and some patients may even be harmed (14,15,19–22). In addition, little is known on the survival benefits of chemotherapy in patients with earlier-stage cancers, as several studies have reported no significant improvement in the outcome (11,23). Therefore, routine chemotherapy after surgery is currently not recommended as the routine treatment for all patients, and its use in cases of earlier-stage GC is still controversial (24). However, a large proportion of patients are still receiving chemotherapy. Therefore, overuse of chemotherapy in clinical practice without substantial improvement in prognosis is possible.

The objectives of this study were to use data from a Chinese multicenter database and the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database to examine the receipt of chemotherapy by age subgroup and to explore the relationship between age differences in chemotherapy and outcome improvement in patients with GC.

METHODS

Patient selection
To construct an international data set using both Western and East Asian patients with GC, all data were collected from 3 hospitals in China (Nanfang Hospital of Southern Medical University [Guangzhou, China], the 1st Affiliated Hospital of Sun Yat-sen University [Guangzhou, China], and Sun Yat-sen University Cancer Center [Guangzhou, China]) and combined with data from the SEER database. The China data sets from 3 hospitals were prospectively maintained, and all messages were extracted from these databases after meticulous verification via internal quality control assessments. We collected data from the China data set of 5,122 consecutive patients who underwent total or partial radical gastrectomy between January 1, 2000, and December 31, 2014. All these patients met the following inclusion criteria: histologically confirmed primary GC, no combined malignant neoplasm, no preoperative history of cancer treatment, more than 15 examined lymph nodes, age between 18 and 85
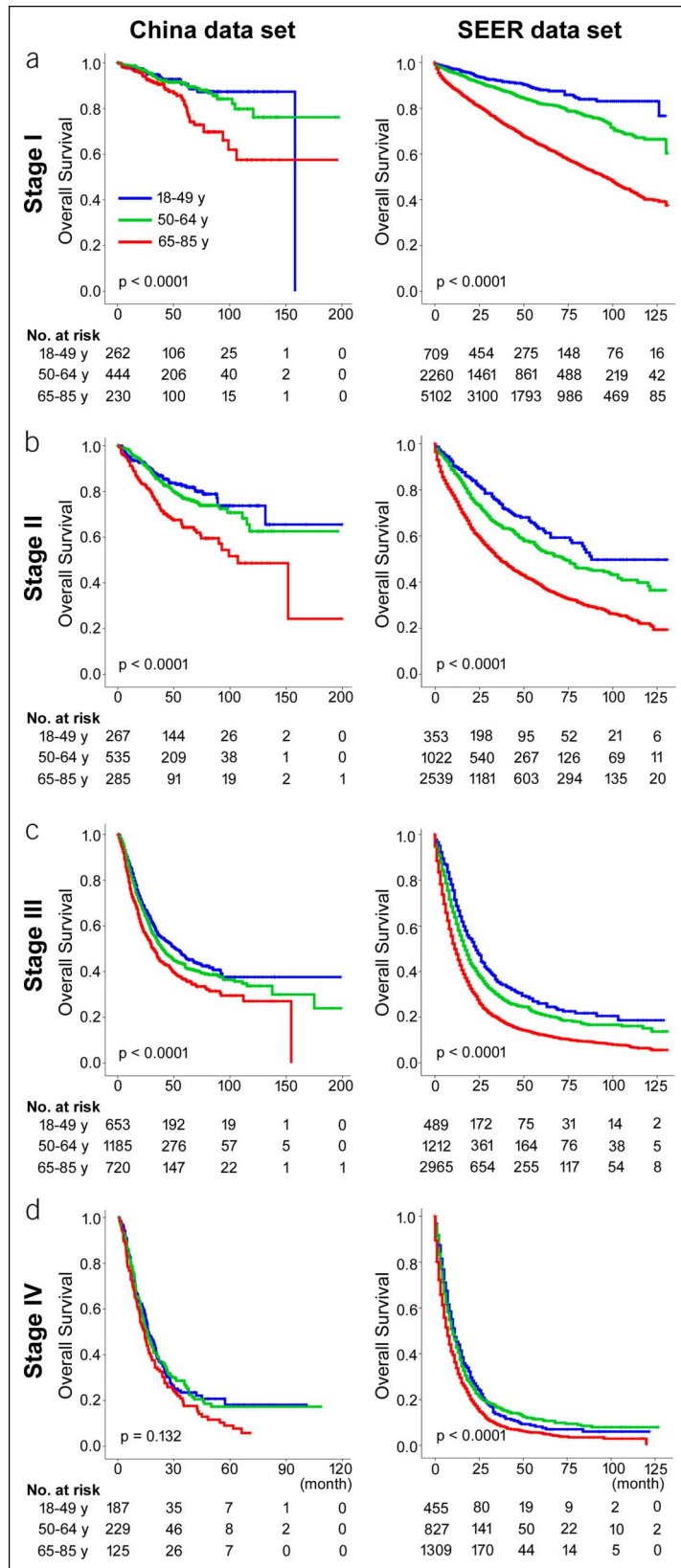
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Figure 1. Overall survival of patients with gastric cancer by age category stratified by tumor stage at diagnosis in China and SEER data sets. China data set (left pane): (**a**) stage I (n = 936); (**b**) stage II (n = 1,087); (**c**) stage III (n = 2,558); and (**d**) stage IV (n = 541). SEER data set (right pane): (**a**) stage I (n = 8,071); (**b**) stage II (n = 3,914); (**c**) stage III (n = 4,666); and (**d**) stage IV (n = 2,591). SEER, Surveillance, Epidemiology, and End Result.

years, and no missing values on any variables. We excluded patients who had received previous treatment with any anticancer therapy. This data set included patient age, sex, race, marital status, insurance status, tumor location, size, preoperative carcinoembryonic antigen and cancer antigen 19-9, tumor differentiation, depth of invasion, lymph node metastasis, distant metastasis, surgery, receipt of chemotherapy, and follow-up data (follow-up duration and survival). Tumor–node–metastasis staging of all patients was restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) Staging Manual of the AJCC/International Union Against Cancer (25). Follow-up data were obtained from the records of the 3 hospitals for patients who were lost to follow-up. The institutional review boards at the 3 cancer centers approved the retrospective analysis of anonymous data, and the informed consent requirement was waved.

To match the time span of the China data set, and considering the changes in AJCC tumor–node–metastasis staging and coding, we extracted only the data between the years 2000 and 2014 from the SEER database. The details are listed in the Supplementary Method (see Supplementary Digital Content 1, http://links.lww.com/CTG/A411).

To increase statistical precision for tabular presentation, patients were classified into 3 subgroups on the basis of age at onset of GC: 18–49 (younger), 50–64 (middle aged), and 65–85 (older) years, after comprehensively considering the population characteristics (1,6,8,26,27). There were 5,122 patients in the China

data set, of whom, 1,369 were younger, 2,393 were middle aged, and 1,360 were older, and there were 31,363 patients in the SEER data set, of whom, 3,553 were younger, 8,558 were middle aged, and 19,252 were older.

The primary end point was overall survival (OS) of patients who received both chemotherapy and surgery compared with patients who received surgery alone. The secondary outcome was the likelihood of receiving chemotherapy.

Statistical analysis

Differences in distributions between the factors examined were assessed with the unpaired, 2-tailed χ^2 test or the Fisher exact test, as appropriate. To compare different age subgroups in the receipt of chemotherapy, we applied multivariable logistic regression models adjusted for potential confounders. A potential confounder was defined as a variable that had association with both age subgroup and chemotherapy, including sex, race, differentiation, tumor location, size, grade, carcinoembryonic antigen, cancer antigen 19-9, marital status, insurance status, high school education, and median household income. Considering that the clinical characteristics and prognosis of patients in different stages may be quite different, we stratified multivariable logistic models based on the GC stage at surgery, and odds ratios (ORs) with 95% confidence intervals (CIs) were generated.

The Kaplan-Meier method and log-rank test were applied to estimate OS. Landmark analysis was performed to estimate the

Table 2. Overall adjusted survival of young (18–49 years) and middle-aged (50–64 years) patients vs older patients (65–75 years) diagnosed with gastric cancer in China data set

Stage	Surgery only		Surgery plus chemotherapy	
	Patients, no. (%)	Adjusted HR (95% CI)[a]	Patients, no. (%)	Adjusted HR (95% CI)[a]
All				
18–49 yr	481 (35.1)	0.570 (0.471–0.690)	888 (64.9)	0.873 (0.739–1.030)
50–64 yr	1,036 (43.3)	0.681 (0.589–0.788)	1,357 (56.7)	0.858 (0.740–0.994)
65–85 yr	743 (54.6)	1 (reference)	617 (45.4)	1 (reference)
Stage I				
18–49 yr	155 (59.2)	0.305 (0.114–0.817)	107 (40.8)	0.778 (0.336–1.798)
50–64 yr	285 (64.2)	0.401 (0.218–0.737)	159 (35.8)	0.643 (0.309–1.341)
65–85 yr	177 (77.0)	1 (reference)	53 (23.0)	1 (reference)
Stage II				
18–49 yr	81 (30.3)	0.273 (0.147–0.508)	186 (69.7)	0.686 (0.418–1.126)
50–64 yr	204 (38.1)	0.496 (0.324–0.760)	331 (61.9)	0.650 (0.431–0.981)
65–85 yr	136 (47.7)	1 (reference)	149 (52.3)	1 (reference)
Stage III				
18–49 yr	177 (27.1)	0.605 (0.471–0.777)	476 (72.9)	0.875 (0.709–1.079)
50–64 yr	440 (37.1)	0.699 (0.580–0.843)	745 (62.9)	1.000 (0.832–1.203)
65–85 yr	369 (51.3)	1 (reference)	351 (48.8)	1 (reference)
Stage IV				
18–49 yr	68 (36.4)	0.734 (0.493–1.093)	119 (63.6)	0.808 (0.546–1.194)
50–64 yr	107 (46.7)	0.837 (0.588–1.192)	122 (53.3)	0.718 (0.502–1.026)
65–85 yr	61 (48.8)	1 (reference)	64 (51.2)	1 (reference)

CI, confidence interval; HR, hazard ratio.

[a]Model adjusted for sex, tumor size, carcinoembryonic antigen, cancer antigen 19-9, differentiation, and location in China data set.

Table 3. Overall adjusted survival of young (18–49 years) and middle-aged (50–64 years) patients vs older patients (65–75 years) diagnosed with gastric cancer in Surveillance, Epidemiology, and End Result data set

Stage	Surgery only		Surgery plus chemotherapy	
	Patients, no. (%)	Adjusted HR (95% CI)[a]	Patients, no. (%)	Adjusted HR (95% CI)[a]
All				
18–49 yr	2,201 (61.9)	0.456 (0.422–0.493)	1,352 (38.1)	0.873 (0.800–0.951)
50–64 yr	5,905 (69.0)	0.580 (0.554–0.607)	2,653 (31.0)	0.887 (0.829–0.950)
65–85 yr	15,934 (82.8)	1 (reference)	3,318 (17.2)	1 (reference)
Stage I				
18–49 yr	613 (86.5)	0.234 (0.176–0.312)	96 (13.5)	0.736 (0.413–1.310)
50–64 yr	2,009 (88.9)	0.399 (0.351–0.453)	251 (11.1)	0.680 (0.470–0.985)
65–85 yr	4,779 (93.7)	1 (reference)	323 (6.3)	1 (reference)
Stage II				
18–49 yr	141 (39.9)	0.424 (0.308–0.582)	212 (60.1)	0.646 (0.479–0.871)
50–64 yr	516 (50.5)	0.606 (0.521–0.706)	506 (49.5)	0.789 (0.643–0.969)
65–85 yr	1,887 (74.3)	1 (reference)	652 (25.7)	1 (reference)
Stage III				
18–49 yr	175 (35.8)	0.598 (0.494–0.724)	314 (64.2)	0.784 (0.658–0.933)
50–64 yr	541 (44.6)	0.726 (0.648–0.813)	671 (55.4)	0.890 (0.783–1.012)
65–85 yr	2,046 (69.0)	1 (reference)	919 (31.0)	1 (reference)
Stage IV				
18–49 yr	150 (33.0)	0.776 (0.634–0.950)	305 (67.0)	0.949 (0.794–1.133)
50–64 yr	336 (40.6)	0.815 (0.705–0.942)	491 (59.4)	0.939 (0.809–1.089)
65–85 yr	858 (65.5)	1 (reference)	451 (34.5)	1 (reference)

CI, confidence interval; HR, hazard ratio.

[a]Model adjusted for sex, race, tumor grade, tumor location, marital status, insurance status, median household income (per $10,000 annual increase), and high school education (per 10% increase) in Surveillance, Epidemiology, and End Result data set.

sensitivity of the Kaplan-Meier survival curves. Multivariable Cox regression methods were applied to assess hazard ratios (HRs) with 95% CIs and to assess the effects of chemotherapy on OS. The multivariable Cox regression was adjusted for the same potential confounding variables as for the logistic regression. Multivariable Cox models were further stratified by the receipt of chemotherapy. All the statistical tests were conducted using R version 3.5.0 (http://www.r-project.org) and SPSS version 22.0 (IBM, Armonk, NY). A 2-sided P value < 0.05 was considered significant.

RESULTS

Tables S1–S2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A411) show the distributions of demographic features and tumor characteristics by age subgroups in China and SEER data sets, respectively. Of the 5,122 patients in the China data set, 3,489 (68.1%) were men, and the median (interquartile range) age of all patients was 57 (49–65) years. Of the 31,363 patients in the SEER data set, 18,115 (57.8%) were men, and the median (interquartile range) age of all patients was 69 (58–77) years. Patients aged 18–49 years were less likely to be male, non-Hispanic White, and have insurance compared with patients aged 50–64 years and 65–85 years in the SEER data set (see Tables S1–S2, Supplementary Digital Content 1, http://links.lww.com/

CTG/A411). More younger-onset patients were initially seen with distant metastases: 13.7% (187/1,369) and 12.8% (455/3,553) of younger-onset tumors were stage IV in China and SEER data sets, respectively, whereas 9.6% (229/2,393), 9.7% (827/8,558) and 9.2% (125/1,360), 6.8% (1,309/19,252) of patients aged 50–64 and 65–85 years were stage IV, respectively ($P < 0.001$). Poor differentiation was more common among younger-onset (18–49 years) cases in both China and SEER data sets. The proportion of receiving postoperative chemotherapy was higher in younger patients (n = 888; 64.9%) than in middle-aged (n = 1,357; 56.7%) and older (n = 617; 45.4%) patients in the China data set ($P < 0.001$). A similar trend was also observed in the SEER data set ($P < 0.001$).

After adjusting for these potential confounder factors, younger patients were found to be more likely to undergo chemotherapy compared with middle-aged and older patients among all GC stages (Table 1). The ORs were 2.151 (95% CI, 1.420–3.259; $P < 0.001$), 2.092 (1.449–3.022; $P < 0.001$), 2.753 (2.178–3.479; $P < 0.001$), and 1.830 (1.128–2.972; $P = 0.014$) for younger patients compared with older patients with stage I, II, III, or IV GC, respectively, in the China data set. In the SEER data set, the ORs were 2.197 (95% CI, 1.696–2.846; $P < 0.001$), 4.161 (3.243–5.339; $P < 0.001$), 4.075 (3.290–5.048; $P < 0.001$), and 4.280 (3.334–5.494; $P < 0.001$) for stage I, II, III, or IV, respectively
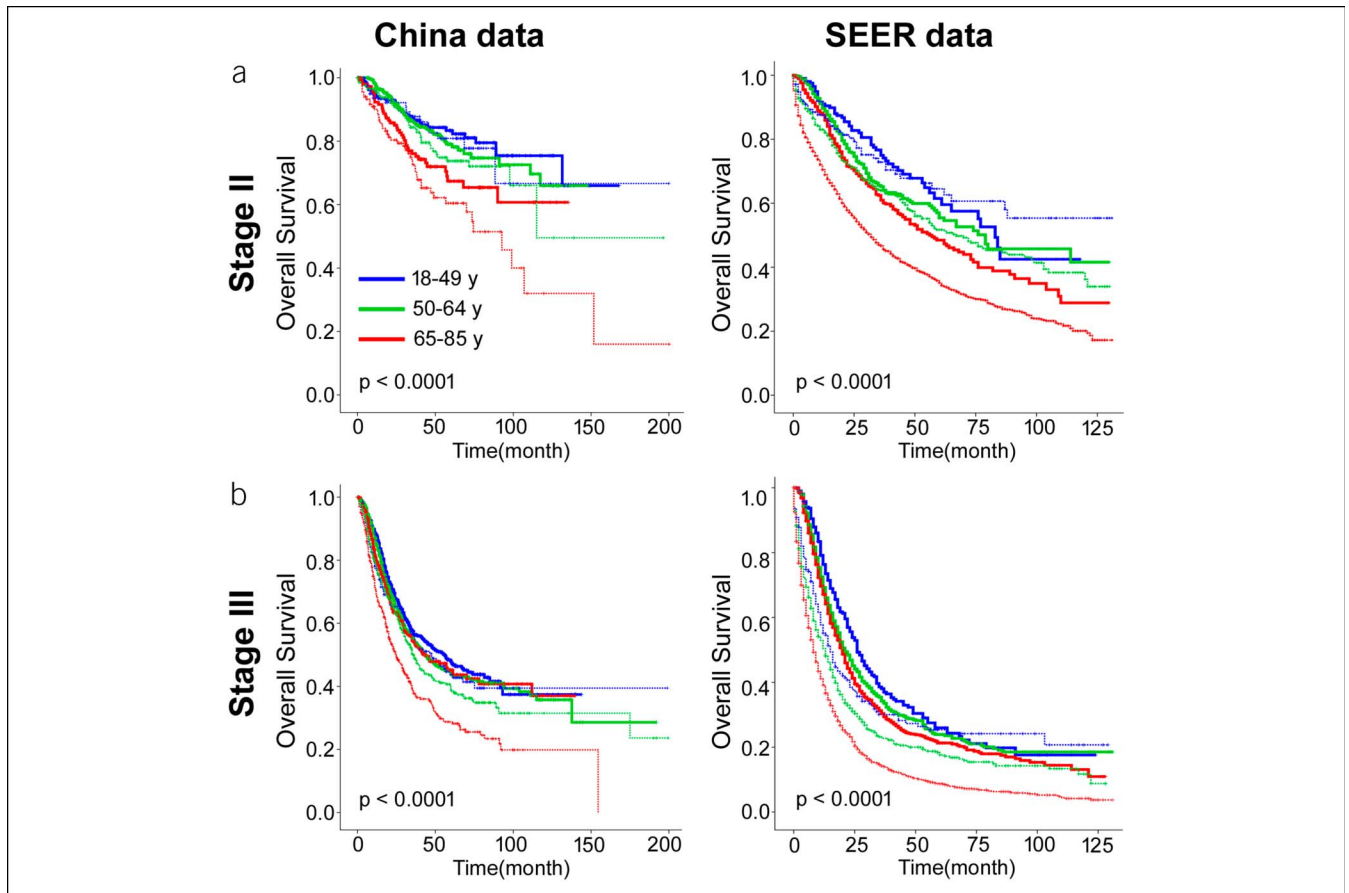
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Figure 2. Kaplan-Meier survival curves for patients with stage II and III gastric cancer in different age groups in China and SEER data sets, which were stratified by the receipt of chemotherapy. China data set (left pane): (**a**) stage II. (**b**) stage III. SEER data set (right pane): (**a**) stage II. (**b**) stage III. CT, chemotherapy; dotted curves, not received chemotherapy; SEER, Surveillance, Epidemiology, and End Result; solid curves, received chemotherapy.

(Table 1). Middle-aged patients with stage I, II, III, or IV GC were also more likely than older patients to receive chemotherapy. The ORs were 1.862 (95% CI, 1.286–2.697; P = 0.001), 1.431 (1.063–1.927; P = 0.018), and 1.762 (1.459–2.129; P < 0.001) for middle-aged patients compared with older patients with stage I, II, or III GC, respectively, in the China data set. In the SEER data set, the ORs were 1.746 (95% CI, 1.458–2.091; P < 0.001), 2.700 (2.294–3.177; P < 0.001), 2.855 (2.467–3.305; P < 0.001), and 2.865 (2.371–3.463; P < 0.001) for middle-aged patients compared with older patients with stage I, II, III, or IV, respectively (Table 1). To explore whether the tendency was different in male patients or in female patients, we performed the same analysis in male and female patients (see Tables S3–S4, Supplementary Digital Content 1, http://links.lww.com/CTG/A411). The results were similar between male and female patients both in the China data set and in the SEER data set (see Tables S3–S4, Supplementary Digital Content 1, http://links.lww.com/CTG/A411). Figure 1 shows survival by GC stage. OS was greatest for younger patients and least for older patients across all stages in the SEER data set (all P < 0.001 in stages I, II, III, and IV, respectively). This trend was consistent in patients with stage I, II, and III disease in the China data set (all P < 0.001 in stages I, II, and III, respectively).

Tables 2 and 3 show OS by GC stage in patients with both surgery and chemotherapy and patients with surgery alone.

Among patients treated with surgery alone, all HR point estimates of younger and middle-aged patients compared with older patients were less than 1 after adjusting for the potential confounders (Tables 2 and 3). Furthermore, a significantly better prognosis was observed in younger (stage I, HR 0.305 [95% CI, 0.114–0.817], P = 0.018; stage II, 0.273 [0.147–0.508], P < 0.001; stage III, 0.605 [0.471–0.777], P < 0.001) and middle-aged (stage I, HR 0.401 [95% CI, 0.218–0.737], P = 0.003; stage II, 0.496 [0.324–0.760], P = 0.001; stage III, 0.699 [0.580–0.843], P < 0.001) patients with stage I, II, and III diseases in the China data set (Table 2) and all stage diseases in the SEER data set (younger: stage I, HR 0.234 [95% CI, 0.176–0.312], P < 0.001; stage II, 0.424 [0.308–0.582], P < 0.001; stage III, 0.598 [0.494–0.724], P < 0.001; stage IV, 0.776 [0.634–0.950], P = 0.014; middle aged: stage I, HR 0.399 [95% CI, 0.351–0.453], P < 0.001; stage II, 0.606 [0.521–0.706], P < 0.001; stage III, 0.726 [0.648–0.813], P < 0.001; stage IV, 0.815 [0.705–0.942], P = 0.006) (Table 3) than their older counterparts. Among patients who received both postoperative chemotherapy and surgery, there were no significant differences in OS among age subgroups in the China data set, with the exception that middle-aged patients with stage II disease had marginally better prognosis than these older patients (HR 0.650; 95% CI, 0.431–0.981). Among all patients of the SEER data set who received chemotherapy and surgery, there were also no significant differences in OS among age subgroups (Table 3). In

the subset analysis according to stage, younger and middle-aged patients had only marginally better survival than did older patients (Table 3). Besides, the HR of patients with both surgery and postoperative chemotherapy was higher than that of patients with surgery alone both in China and SEER data sets, given age subgroup and GC stage. We further conducted the same analysis in male and female patients (see Tables S5–S8, Supplementary Digital Content 1, http://links.lww.com/CTG/A411). Similar results were observed between male and female patients both in the China data set and in the SEER data set (see Tables S5–S8, Supplementary Digital Content 1, http://links.lww.com/CTG/A411).

Furthermore, we investigated the survival benefits from chemotherapy among younger, middle-aged, and older patients. A test for an interaction between age groups and chemotherapy indicated that in both stage II and III diseases, the survival benefit from chemotherapy was superior among older patients (China data set: stage II, HR 0.681 [0.447–1.038], $P = 0.074$; stage III, 0.631 [0.517–0.769], $P < 0.001$; SEER data set: stage II, HR 0.620 [0.540–0.712], $P < 0.001$; stage III, 0.523 [0.477–0.574], $P < 0.001$; all $P < 0.0001$ for interaction; see Table S9, Supplementary Digital Content 1, http://links.lww.com/CTG/A411) compared with that among younger and middle-aged patients. The corresponding Kaplan-Meier curves of patients with stage II and stage III GC, which comprehensively compared younger, middle-aged, with older patients by treatment, are shown in Figure 2 and Figure S1 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A411). Two landmark time points (12 months and 36 months) were determined to account for immortal time bias in this study (see Figure S2 and Figure S3, Supplementary Digital Content 1, http://links.lww.com/CTG/A411). The results of the subgroup analysis using age groups showed that chemotherapy could significantly increase OS time in the older patients of China and SEER data sets (stage II, $P = 0.072$ and $P < 0.0001$; stage III, $P < 0.0001$ and $P < 0.0001$, respectively), but there were no significant effects in the younger and middle-aged patients with stage II GC (China data set: $P = 0.675$ and $P = 0.284$; SEER data set: $P = 0.910$ and $P = 0.083$, respectively; see Figure S1, Supplementary Digital Content 1, http://links.lww.com/CTG/A411) and in the younger patients with stage III GC in the China data set ($P = 0.255$). As Figure S2 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A411) shows, when performing the landmark analysis to adjust the immortal time bias, we found similar results suggesting that chemotherapy could significantly increase OS time in older patients of both China and SEER data sets, and there still were no significant effects of chemotherapy in younger and middle-aged patients of both 2 data sets. Consequently, these results suggest that younger patients obtain fewer survival benefits from chemotherapy than older patients, although younger patients are much more likely to receive chemotherapy.

DISCUSSION

This study explored whether younger and middle-aged patients with GC were exposed to overuse of chemotherapy in the China multicenter data set and the SEER data set. We observed that younger and middle-aged patients were more likely than older patients aged 65–85 years to receive chemotherapy, regardless of the GC stage at diagnosis, indicating a tendency of more intense treatments for younger patients. Younger and middle-aged adults who received only surgery had better prognosis compared with older patients aged 65–85 years; however, almost no significant

differences of OS were observed between younger/middle-aged patients and older patients who received both postoperative chemotherapy and surgery after adjusting for these potential confounders, especially in the China data set. In addition, younger and middle-aged patients obtained fewer survival benefits from chemotherapy than those of their older counterparts. Besides, the tendency of this impact on chemotherapy in younger and middle-aged patients with GC was similar in men or in women compared with older patients. Our study suggested that overuse of chemotherapy for younger adults with GC did not bring about additional survival benefits.

With regard to young and older patients, no clear-cut distinction exists now. Previous reports used 30, 40, 45, and 50 years as thresholds for younger patients and 65, 70, 75, and 80 years as thresholds for older patients (8,12,13,28,29). Data from the National Bureau of Statistics of China showed that the average life span in China was 72.38 years for males and 77.37 years for females in 2010, and patients aged ≥ 65 years accounted for 8.87% of the total population (28). Guan et al. found that young patients who were aged 30–50 years at diagnosis had the best survival rate (8), whereas the results of some studies suggest poorer survival in the young (9,10). Al-Refaie et al. found that older patients (aged ≥ 65 years) were associated with worse cancer-specific mortality (29). However, Karaca et al. (13) showed that no significant difference was detected in survival between older patients aged ≥ 65 years and patients aged < 65 years. In this study, after comprehensively considering the patients' characteristics of China and SEER data sets and the prior studies (1,6,8,13,26,28,29), to increase statistical precision for tabular presentation, we categorized patients into 3 subgroups on the basis of age at diagnosis: 18–49 (younger), 50–64 (middle aged), and 65–85 (older) years. Significant difference was observed in OS among the 3 age groups (Figure 1). Moreover, OS was best for younger patients and worst for older patients across all stages in the SEER data set and stage I, II, and III disease in the China data set (Figure 1).

Recently, survival improvement has been shown in patients with GC, mostly owing to development of drug treatment (16,30–32). Postoperative chemotherapy has been recommended as a routine therapy after surgery for patients with advanced GC in East Asia (14,16). Nevertheless, administration of postoperative chemotherapy to every stage II or stage III patient is needless and may even have an adverse effect for a group of patients with GC (14,16,20,21,33–37). Our findings showed higher chemotherapy use in younger adults with GC compared with older patients with stages II and III as well as stages I and IV. We also found that almost 40.8% of the younger adults with stage I disease in the China data set and 13.5% of those in the SEER data set received postoperative chemotherapy, and greater than 60% of the younger adults with stage II disease both in China and SEER data set. These practices may indicate overtreatment, especially in Chinese patients, because previous and current guidelines do not definitely recommend chemotherapy in stage I patients and still indicate some disputes of chemotherapy in some stage II patients (16,33,38). Decision making concerning chemotherapy involves clinician's recommendation and patients' acceptance. Clinicians are often disinclined to recommend chemotherapy to 65–85-year (older) patients due to higher prevalence of those comorbid diseases, side effects of the chemotherapy, and chronological age itself (12,29,39). Attention is even less likely to be paid to younger patients; therefore, clinicians could be more likely to recommend

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giving chemotherapy (40). Besides, the patient's decision of undergoing postoperative chemotherapy or not could be influenced by geographic and financial barriers to care and involvement in the decision-making procedure, which could also be different among age groups (12,39–41). Furthermore, younger adults preferred to know more information about chemotherapy and this disease and may want to be more involved in therapy decision making (42,43).

Previous studies have mostly concentrated on the elderly, indicating possible undertreatment, and very few examined young patients with cancer (13,39,44). So far, reports about chemotherapy in young patients with GC have been confined to only few small retrospective studies. Our study demonstrated a higher treatment of postoperative chemotherapy for younger patients in the Chinese multicenter data set and the population-based SEER data set. However, although younger patients with GC were much more likely to have postoperative chemotherapy, their OS was not relatively increased with the addition of chemotherapy, indicating overuse of chemotherapy among younger patients. Thus, the results may have great clinical and economic application value. Patients who receive chemotherapy are susceptible to its adverse effects and toxicity and their life quality might decrease (38). Therefore, patients might have reduced physical, functional, emotional, and social well-being, although these changes may be alleviated over time (45–47). Besides the effects on life quality, overuse of chemotherapy raises socioeconomic burdens on account of the relatively high cost of chemotherapy for GC (48). Consequently, rational application of chemotherapy in GC treatment needs to be discussed and assessed in further studies.

There were also some limitations in our study. First, the study was conducted retrospectively, and the SEER data set and the China data set were included in different periods, making it impressionable to the inherent biases of this kind of study format, such as the different confounders between the China data set and the SEER data set, because the China data set does not record some factors such as marital status and insurance status, and this unremovable issue needs to be validated by further research. Second, the record of the death reason was not clear, so we use the OS instead of cancer-specific survival or cancer-free survival as a primary outcome, and this may ignore the problem of non–cancer-specific mortality, which might bias the survival outcomes, for example, death caused by comorbidities, especially for patients with increasing age. Third, the existence of comorbidities (i.e., nutritional status and general health status) is an unfavorable factor for older patients, and the potential confounding factors were not adjusted in this study because of limited data. Obviously, these results need to be further validated in well-designated multicenter prospective clinical trials.

Younger and middle-aged adults with GC received more postoperative chemotherapy, but they showed only minimal increment of adjusted OS compared with the older counterparts who received less chemotherapy, especially in the China data set. This mismatch indicates that attention should be paid to long-term GC survivorship in younger adults with GC because they probably face survivorship needs that are different from their older counterparts.

CONFLICTS OF INTEREST

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Specific author contributions: Yuming Jiang, MD, PhD, Jingjing Xie, MD, and Weicai Huang, MD, PhD, contributed equally to this work. Conception and design: Z.Z., S.C., and G.L. Financial support: T.L. and G.L. Administrative support: Y.H., J.Y., and G.L. Provision of study materials or patients: Y.J., T.L., Y.H., W.L., and J.Y. Collection and assembly of data: Y.J., W.H., H.C., S.X., C.C., and Z.S. Data analysis and interpretation: Y.J., J.X., H.C., S.X., T.L., C.C., Y.H., and J.Y. Manuscript writing: all authors. Final approval of the manuscript: all authors.

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