Chemotherapy for Metastatic Gastric Cancer: Does Age Matter? A Single-Center, Retrospective, Real-World Study

Clinical Medicine Insights: Oncology
Volume 16: 1–12
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DOI: 10.1177/11795549221123617
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ABSTRACT

BACKGROUND: Palliative chemotherapy is the preferred standard of care for patients with metastatic gastric cancer (mGC). It remains uncertain whether older patients with mGC would benefit from palliative chemotherapy. This study aimed to investigate the clinical impact of palliative chemotherapy in older patients with mGC.

METHODS: This single-institute, retrospective, and real-world study included 428 patients with mGC between January 2009 and December 2019. Among them, 306 who received palliative chemotherapy were further stratified into 2 groups according to age: ≤70 (n = 236) and >70 (n = 70) years. The clinical demographics, outcomes, and hematologic toxicities of chemotherapy were compared between the 2 groups. Prognostic factors were determined using the Cox proportional hazards model.

RESULTS: Of the screened 428 patients, older patients had worse overall survival (OS) than younger patients. Among patients who received chemotherapy (n = 306), patients aged >70 and ⩽70 years had comparable progression-free survival (PFS) and OS. The incidence of severe hematologic toxicity was similar between the 2 groups. The Eastern Cooperative Oncology Group performance status of 2 or more metastatic sites, elevated carbohydrate antigen 19-9 level, high neutrophil-to-lymphocyte ratio (NLR), and undergoing palliative gastrectomy were independent prognostic factors for OS. Notably, age >70 years was not a significant factor for poor OS.

CONCLUSIONS: Older age of >70 years might not be considered an obstacle to administering palliative chemotherapy to patients with mGC.

KEYWORDS: Older patients, gastric cancer, geriatric oncology, overall survival, performance status

RECEIVED: April 7, 2022. **ACCEPTED:** August 10, 2022.

TYPE: Gastrointestinal Tumor Heterogeneity and New Treatment Strategies-Original Research Article

FUNDING: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by grants from TCVGH-1113701A.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: C-LJT received an honorarium and consulting fees from Novartis, Roche, Takeda, Johnson & Johnson, Amgen, BMS Celgene, Kirin, and MSD. The other authors declare that they have no conflicts of interest.

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Introduction

Gastric cancer is the third leading cause of cancer-related deaths worldwide. According to the GLOBOCAN 2020 database, gastric cancer is the most frequently diagnosed in 19 countries, and 60% are in Eastern Asia.[1] Owing to the success of *Helicobacter pylori* eradication, the incidence of gastric adenocarcinoma in Taiwan significantly decreased from 13.56 per 100 000 persons in 1996 to 9.82 per 100 000 persons in 2013.[2] However, gastric cancer remains one of the top 10 causes of cancer mortality. The mean age of gastric cancer diagnosis in Taiwan was 67.2 years from 1996 to 2013. According to the Taiwan Cancer Registry, >40% of newly diagnosed patients with gastric cancer are >70 years of age. Furthermore, these patients have a poor prognosis.[2,3]

Some studies have elucidated the characteristics and surgical outcomes of resectable gastric cancer in older patients and have reported that older patients are more likely to have an advanced-stage disease and worse 5-year overall survival (OS). Older patients with good performance status (PS) may benefit from surgical intervention.[4,5] However, few studies have explored the clinical features and outcomes of older patients with metastatic gastric cancer (mGC) receiving palliative chemotherapy.

Current treatment guidelines for mGC have proposed combined chemotherapeutic agents as first-line treatment.[6,7] Most

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of these therapeutic guidelines are based on prospective and randomized controlled studies. However, patients aged >65 years were underrepresented in these trials.[8,9] In a recently published phase III study, CheckMate 649, focusing on gastric and esophageal adenocarcinomas, the median age of 792 patients undergoing chemotherapy was only 61 (interquartile range, 53-68) years.[10] Since older patients are more likely to be excluded from clinical trials due to their propensity to exhibit increased comorbidities and worse PS, the role of palliative chemotherapy for older patients with mGC in a real-world setting is unclear and needs further investigation.

Therefore, this study aimed to investigate the clinical impact of palliative chemotherapy in older patients with mGC by comparing the clinical characteristics, therapeutic strategies, treatment responses, and outcomes of patients aged >70 and ≤70 years.

Patients and Methods

Patients

The medical records of 581 consecutive patients with mGC or gastroesophageal junction cancer diagnosed between January 2009 and December 2019 at Taichung Veterans General Hospital were retrospectively reviewed. The eighth edition of the American Joint Committee on Cancer (AJCC) staging system was used to determine the cancer stage.[11] Patients without pathology reports (n = 6) and treated at other hospitals but no available medical records (n = 7) and with non-adenocarcinoma cancer (n = 22), tumor origin other than the stomach (n = 5), no evidence of metastasis (n = 10), follow-up of <3 months (n = 97), and any other non-gastric metastatic cancer (n = 6) were excluded. Furthermore, 428 patients were included in the analysis. This study was conducted according to the principles of the Declaration of Helsinki. The institutional review board of Taichung Veterans General Hospital approved the study and waived the requirement for informed consent because of its retrospective design (No. CE21334A).

Definitions and outcome measurements

The patients were categorized into ≤70 years, considered as the young group and >70 years, the old group. The age was classified based on ESMO Clinical Practice Guidelines and previous studies.[6,12] The patients' PS was measured using the Eastern Cooperative Oncology Group (ECOG) criteria.[13] The age-adjusted Charlson comorbidity index (CCI) is a combination of the age equivalence index and CCI.[14,15] The tumor location was categorized as the gastroesophageal junction, cardia, fundus/body, antrum, pylorus, entire stomach, or anastomosis site based on the endoscopy report. Gastric cancer was categorized into well-differentiated (Grade 1), moderately differentiated (Grade 2), and poorly differentiated (Grade 3) according to the AJCC eighth edition. Human epidermal growth factor receptor 2 (HER2) overexpression was determined using immunohistochemistry staining, and *H pylori* infection was assessed using Giemsa staining. The neutrophil-to-lymphocyte ratio (NLR) was obtained by dividing the peripheral neutrophil count (number/μL) by the peripheral lymphocyte count (number/μL).[16] The prognostic nutrition index (PNI) was calculated using the formula: 10 × serum albumin concentration (g/dL) + 0.005 × peripheral lymphocyte count (number/μL).[17] The cut-off value in the current study was set as 4.5 for NLR and 40 for PNI, according to the median value in our cohort and previous studies.[18,19]

This study's primary endpoint was OS, while secondary endpoints were progression-free survival (PFS), disease control rate (DCR), and adverse events. OS was defined as the time from the date of diagnosis to death from any cause. PFS was defined as the time from the date of diagnosis to disease progression or death. If the date of death or disease progression was uncertain, it was censored at the date of the last follow-up. The cut-off day of data analysis was February 1, 2021. Tumor response was measured according to the Response Evaluation Criteria in Solid Tumors v1.1.[20] The Common Terminology Criteria for Adverse Events v5.0 was used to evaluate the severity of hematologic toxicities caused by chemotherapy.

Statistical analyses

The chi-squared test or Fisher's exact test was performed to analyze the categorical variables, while the Mann-Whitney *U* test was used for continuous variables. The Kaplan-Meier method was used to calculate PFS and OS, and differences were compared using the log-rank test. A Cox proportional hazards model was used to identify prognostic factors, quantified as hazard ratios (HRs) with 95% confidence intervals (CIs). A propensity score matching analysis was performed to reduce treatment selection bias. Subgroup analyses were conducted in ECOG PS 0-2, ECOG PS 3-4, receiving single-agent and combination chemotherapies. Statistical significance was set at a *P*-value of less than .05. SPSS (version 22.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Clinical characteristics and outcome comparison of the entire cohort

Briefly, the old group (>70 years of age) and young group (≤70 years of age) were comparable in terms of body mass index, the primary site of cancer, the number of metastatic sites, HER2 overexpression, *H pylori* infection, carcinoembryonic antigen (CEA) levels, carbohydrate antigen (CA) 19-9 levels, and NLR. However, the percentage of men was higher in the old group than in the young group (68.8% vs 57.4%; $P = .03$). Additionally, patients in the old group had a higher ECOG PS of 2-4 (48.6% vs 18.0%; $P < .001$), age-adjusted CCI of ≥4 (74.3% vs 10.2%; $P < .001$), and PNI ≤ 40 (58.1% vs 46.7%; $P = .039$) than those in the young group. In contrast, the incidences of poorly differentiated histology (85.6% vs 75.9%; $P = .025$) and signet-ring cell features (45.3% vs 30.5%; $P = .007$)

were higher in the young group than in the old group. The proportion of patients for mGC treatment undergoing tumor resection was similar between the 2 groups, while a smaller proportion of patients received palliative chemotherapy in the old group (48.6% vs 83.1%; $P < .001$) (Table 1).

The median OS of 428 patients was 8.7 (95% CI: 7.4-10.0) months. Moreover, patients in the young group had a significantly longer median OS than those in the old group (9.8 vs 6.6 months; $P = .002$) (Figure 1).

Clinical characteristics and outcome comparison of the old group

In the old group, 70 patients received chemotherapy, and 74 did not. Patients who did not receive chemotherapy were older and had higher ECOG PS, age-adjusted CCI, and NLR (Supplementary Table S1). Patients who received chemotherapy had significantly longer PFS (7.6 vs 1.9 months; $P < .001$) and OS (12.1 vs 1.9 months; $P < .001$) (Supplementary Figure S1).

Characteristics of patients undergoing palliative chemotherapy

This study further stratified 306 patients who received palliative chemotherapy into old (n = 70) and young groups (n = 236) according to the age at pathological diagnosis,[21-23] and compared patients' characteristics and outcomes between the groups. The results showed that a higher proportion of patients had ECOG PS of 2-4 (25.7% vs 9.3%; $P < .001$) and age-adjusted CCI of ≥4 (61.4% vs 7.2%; $P < .001$) in the old group than in the young group. Contrastingly, a higher proportion of patients had signet-ring features in the young group than in the old group (44.9% vs 24.6%; $P = .006$). For first-line chemotherapy, patients in the old group were more likely to receive monotherapy than those in the young group (38.6% vs 11.4%; $P < .001$). However, the old group had a lower chance of receiving second-line or later-line palliative chemotherapy than the young group (30.0% vs 47.0%; $P = .017$) (Table 2).

Comparison of response and survival among patients after palliative chemotherapy

The old and young groups had a comparable DCR after first-line palliative chemotherapy (69% vs 76%; $P = .471$) (Figure 2). Moreover, the median PFS for the old and young groups were 7.6 (95% CI: 6.0-9.2) months and 7.0 (95% CI: 6.1-7.8) months, respectively (HR: 0.94; 95% CI: 0.70-1.26, $P = .690$) (Figure 3A). Similarly, the median OS in the old group was not significantly different from that in the young group (12.1 vs 11.9 months; $P = .944$) (Figure 3B).

The propensity-matched cohort included 76 patients; 38 (50%) were >70 years of age. The baseline characteristics were balanced between groups after matching (Supplementary Table S2). No significant difference in OS was observed between the 2 groups (Supplementary Figure S2). In the subgroup analysis, the OS was similar between the 2 groups in patients with ECOG PS 0-2, ECOG PS 3-4, receiving single-agent, and combination chemotherapies (Supplementary Figure S3, S4).

Prognostic factors for patients undergoing palliative chemotherapy

In the univariate analysis, ECOG PS of ≥2 (HR: 2.05; 95% CI: 1.52-2.76; $P < .001$), 2 or more metastatic sites (HR: 2.47; 95% CI: 1.85-3.30; $P < .001$), poorly differentiated histology (HR: 1.64; 95% CI: 1.08-2.48; $P = .021$), *H pylori* infection (HR: 1.54; 95% CI: 1.06-2.25; $P = .023$), CA 19-9 ≥ 34 U/mL (HR: 1.75; 95% CI: 1.26-2.43; $P = .001$), and NLR > 4.5 (HR: 2.00; 95% CI: 1.50-2.67; $P < .001$) were associated with worse OS. Contrastingly, patients who underwent palliative gastrectomy had a better OS (HR: 0.44; 95% CI: 0.33-0.59; $P < .001$) (Table 3). The multivariate analyses were used to validate this result and showed that ECOG PS of ≥2 (HR: 1.63; 95% CI: 1.08-2.46; $P = .020$), 2 or more metastatic sites (HR: 2.03; 95% CI: 1.37-2.98; $P < .001$), CA 19-9 ≥ 34 U/mL (HR: 1.51; 95% CI: 1.02-2.24; $P = .038$), and NLR > 4.5 (HR: 2.00; 95% CI: 1.38-2.89; $P < .001$) remained poor prognostic factors. Notably, palliative gastrectomy (HR: 0.62; 95% CI: 0.41-0.93; $P = .021$) was a good prognostic factor for patients with mGC undergoing palliative chemotherapy (Table 3).

Hematologic adverse events

The young group had a higher incidence of all-grade neutropenia (32.6% vs 18.6%). However, the incidences of Grade 3-4 neutropenia (10.6% vs 10.0%; $P = 1.000$) and febrile neutropenia (3.4% vs 2.9%; $P = 1.000$) were not significantly different between the groups. Additionally, the incidences of Grade 3-4 anemia (24.2% vs 20.0%; $P = .574$) and thrombocytopenia (11.4% vs 5.7%; $P = .242$) were comparable between the 2 groups (Table 4). The causes of chemotherapy discontinuation were similar between the 2 groups (Supplementary Figure 5S).

Discussion

This study demonstrated that patients aged >70 years with mGC had worse OS than those aged ≤70 years. However, for patients who received palliative chemotherapy in a real-life setting, DCR, PFS, and OS were comparable between the old and young groups. Factors, such as the ECOG PS of 2-4, 2 or more metastatic sites, elevated CA 19-9 level, NLR > 4.5, and not undergoing palliative gastrectomy were found to be associated with an inferior OS. Notably, age > 70 years was not a poor prognostic factor, suggesting that age might not be an obstacle to administering palliative chemotherapy to patients with mGC.

A recent study of the Taiwan Cancer Registry database, including 5599 patients with mGC, reported that age is a poor prognostic factor to OS. The proportion of patients receiving chemotherapy in younger patients was 65% but decreased to

Table 1. Patient characteristics stratified according to age.

	TOTAL (N = 428)		⩽70YEARS (N = 284)		>70YEARS (N = 144)		*P*
Age, median (range, years)	64	(54-75)	57	(49-64)	78	(74-84)	<.001
Sex, n (%)							.030
Male	262	(61.2)	163	(57.4)	99	(68.8)	
Female	166	(38.8)	121	(42.6)	45	(31.2)	
BMI, n/total n (%)							.814
<18.5	64/401	(16.0)	44/271	(16.2)	20/130	(15.4)	
18.5-23.9	225/401	(56.1)	154/271	(56.8)	71/130	(54.6)	
⩾24.0	112/401	(27.9)	73/271	(26.9)	39/130	(30.0)	
ECOG performance status, n (%)							<.001
0	221	(51.6)	182	(64.1)	39	(27.1)	
1	86	(20.1)	51	(18.0)	35	(24.3)	
2-4	121	(28.3)	51	(18.0)	70	(48.6)	
aCCI, n (%)							<.001
0-3	292	(68.2)	255	(89.8)	37	(25.7)	
⩾4	136	(31.8)	29	(10.2)	107	(74.3)	
Primary site, n/total n (%)							.131
Gastroesophageal junction	23/392	(5.9)	16/255	(6.3)	7/137	(5.1)	
Cardia	36/392	(9.2)	20/255	(7.8)	16/137	(11.7)	
Fundus/body	161/392	(41.1)	118/255	(46.3)	43/137	(31.4)	
Antrum	132/392	(33.7)	77/255	(30.2)	55/137	(40.1)	
Pylorus	13/392	(3.3)	7/255	(2.7)	6/137	(4.4)	
Entire	5/392	(1.3)	3/255	(1.2)	2/137	(1.5)	
Anastomosis site	22/392	(5.6)	14/255	(5.5)	8/137	(5.8)	
Burden of metastatic disease, n (%)							.323
1	270	(63.1)	174	(61.3)	96	(66.7)	
⩾2	158	(36.9)	110	(38.7)	48	(33.3)	
Histologic grade, n/total n (%)							.025
Grade 1-2	70/397	(17.6)	38/264	(14.4)	32/133	(24.1)	
Grade 3	327/397	(82.4)	226/264	(85.6)	101/133	(75.9)	
Signet-ring feature, n/total n (%)							.007
No	231/387	(59.7)	140/256	(54.7)	91/131	(69.5)	
Yes	156/387	(40.3)	116/256	(45.3)	40/131	(30.5)	
HER2 overexpression, n/total n (%)							.100
0, 1+, 2+	225/262	(85.9)	156/176	(88.7)	69/86	(80.2)	
3+	37/262	(14.1)	20/176	(11.4)	17/86	(19.8)	
Helicobacter pylori infection, n/total n (%)							.853

(Continued)

Table 1. (Continued)

	TOTAL (N = 428)		⩽70 YEARS (N = 284)		>70 YEARS (N = 144)		*P*
No	277/339	(81.7)	177/218	(81.2)	100/121	(82.6)	
Yes	62/339	(18.3)	41/218	(18.8)	21/121	(17.4)	
CEA level, n/total n (%)							.100
Normal (<5 U/mL)	218/381	(57.2)	155/257	(60.3)	63/124	(50.8)	
Elevated (⩾5 U/mL)	163/381	(42.8)	102/257	(39.7)	61/124	(49.2)	
CA 19-9 level, n/total n (%)							1.000
Normal (<34 U/mL)	177/335	(52.8)	120/228	(52.6)	57/107	(53.3)	
Elevated (⩾34 U/mL)	158/335	(47.2)	108/228	(47.4)	50/107	(46.7)	
NLR, n/total n (%)							.414
⩽4.5	200/421	(47.5)	137/279	(49.1)	63/142	(44.4)	
>4.5	221/421	(52.5)	142/279	(50.9)	79/142	(55.6)	
PNI, n/total n (%)							.039
⩽40	206/408	(50.5)	127/272	(46.7)	79/136	(58.1)	
>40	202/408	(49.5)	145/272	(53.3)	57/136	(41.9)	
Palliative gastrectomy, n (%)							.439
No	264	(61.7)	171	(60.2)	93	(64.6)	
Yes	164	(38.3)	113	(39.8)	51	(35.4)	
Palliative chemotherapy, n (%)							<.001
No	122	(28.5)	48	(16.9)	74	(51.4)	
Yes	306	(71.5)	236	(83.1)	70	(48.6)	

Abbreviations: aCCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index.

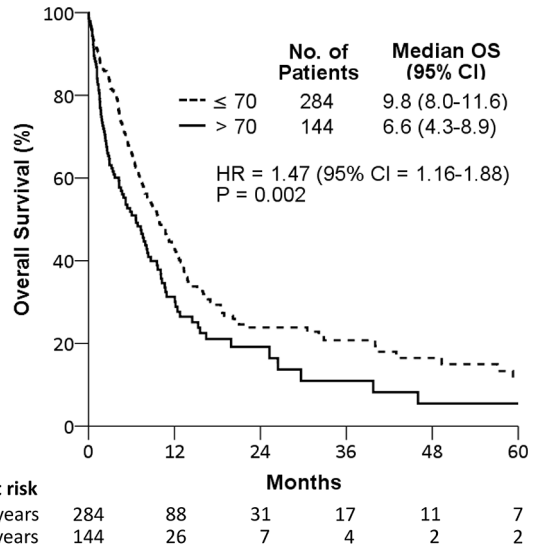

Figure 1. OS comparison among older (>70 years) and younger patients (⩽70 years) with mGC. CI indicates confidence interval; HR, hazard ratio; OS, overall survival.

39% in patients >75 years.[24] These findings agree with our cohort. In this study, older patients are more likely to have poorer performance status, nutrition, and more comorbidities. These factors might lead to worse survival in the old group (Table 1). Cavanagh et al[25] investigated patients with advanced gastroesophageal adenocarcinoma treated with best supportive care alone and reported poorer ECOG PS as an independent factor associated with worse OS. However, if old patients are not fragile and can receive chemotherapy after assessment, does palliative chemotherapy provide a survival benefit? This study's data showed that old patients who received chemotherapy had remarkably better PFS and OS compared with old patients who did not receive chemotherapy (Supplementary Figure S1). Previous studies have compared chemotherapeutic efficacy in patients with various metastatic gastrointestinal cancers according to age. A retrospective analysis of 22 European trials, which included 3825 patients with metastatic colorectal cancers treated with 5-fluorouracil (5-FU)-containing regimens, showed that patients in the ⩾70 and <70 year-old groups had similar overall

Table 2. Characteristics of patients who received chemotherapy.

	TOTAL (N = 306)		⩽70YEARS (N = 236)		>70YEARS (N = 70)		*P*-VALUE
Age, median (range, years)	60	(52-69)	57	(48-63)	76	(73-79)	<.001
Sex, n (%)							.167
Male	177	(57.8)	131	(55.5)	46	(65.7)	
Female	129	(42.2)	105	(44.5)	24	(34.3)	
BMI, n/total n (%)							.665
<18.5, n (%)	43/298	(14.4)	35/230	(15.2)	8/68	(11.8)	
18.5-23.9, n (%)	169/298	(56.7)	131/230	(57.0)	38/68	(55.9)	
⩾24.0, n (%)	86/298	(28.9)	64/230	(27.8)	22/68	(32.4)	
ECOG performance status, n (%)							<.001
0	199	(65.0)	168	(71.2)	31	(44.3)	
1	67	(21.9)	46	(19.5)	21	(30.0)	
2-4	40	(13.1)	22	(9.3)	18	(25.7)	
aCCI, n (%)							<.001
0-3	246	(80.4)	219	(92.8)	27	(38.6)	
⩾4	60	(19.6)	17	(7.2)	43	(61.4)	
Primary site, n/total n (%)							.358
Gastroesophageal junction	17/279	(6.1)	13/213	(6.1)	4/66	(6.0)	
Cardia	24/279	(8.6)	17/213	(8.0)	7/66	(10.4)	
Fundus/body	117/279	(41.9)	97/213	(45.8)	20/66	(29.9)	
Antrum	95/279	(34.1)	65/213	(30.7)	30/66	(44.8)	
Pylorus	7/279	(2.5)	5/213	(2.4)	2/66	(3.0)	
Entire	4/279	(1.4)	3/213	(1.4)	1/66	(1.5)	
Anastomosis site	15/279	(5.4)	12/213	(5.7)	3/66	(4.5)	
Burden of metastatic disease, n (%)							.138
1	198	(64.7)	147	(62.3)	51	(72.9)	
⩾2	108	(35.3)	89	(37.7)	19	(27.1)	
Histologic grade, n/total n (%)							.057
Grade 1-2	52/289	(18.0)	34/221	(15.4)	18/68	(26.5)	
Grade 3	237/289	(82.0)	187/221	(84.6)	50/68	(73.5)	
Signet-ring feature, n/total n (%)							.006
No	167/279	(59.9)	118/214	(55.1)	49/65	(75.4)	
Yes	112/279	(40.1)	96/214	(44.9)	16/65	(24.6)	
HER2 overexpression, n/total n (%)							.068
0, 1+, 2+	164/190	(86.3)	131/147	(89.1)	33/43	(76.7)	
3+	26/190	(13.7)	16/147	(10.9)	10/43	(23.3)	
H pylori infection, n/total n (%)							.480

(Continued)

Table 2. (Continued)

	TOTAL (N = 306)		≤70 YEARS (N = 236)		>70 YEARS (N = 70)		*P*-VALUE
No	193/240	(80.4)	144/182	(79.1)	49/58	(84.5)	
Yes	47/240	(19.6)	38/182	(20.9)	9/58	(15.5)	
CEA level, n/total n (%)							.055
Normal (<5 U/mL)	164/283	(58.0)	133/217	(61.3)	31/66	(47.0)	
Elevated (≥5 U/mL)	119/283	(42.0)	84/217	(38.7)	35/66	(53.0)	
CA 19-9 level, n/total n (%)							.713
Normal (<34 U/mL)	135/245	(55.1)	103/190	(54.2)	32/55	(58.2)	
Elevated (≥34 U/mL)	110/245	(44.9)	87/190	(45.8)	23/55	(41.8)	
NLR, n/total n (%)							.870
≤4.5	161/300	(53.7)	123/231	(53.0)	38/69	(55.1)	
>4.5	140/300	(46.7)	109/231	(47.0)	31/69	(44.9)	
PNI, n/total n (%)							.503
≤40	136/293	(46.4)	102/226	(45.1)	34/67	(50.7)	
>40	157/293	(53.6)	124/226	(54.9)	33/67	(49.3)	
Palliative gastrectomy, n (%)							.158
No	169	(55.2)	136	(57.6)	33	(47.1)	
Yes	137	(44.8)	100	(42.4)	37	(52.9)	
First-line chemotherapy, n (%)							<.001
Single agent	54	(17.6)	27	(11.4)	27	(38.6)	
Combination	252	(82.4)	209	(88.6)	43	(61.4)	
Line of chemotherapy, n (%)							.017
1	174	(56.9)	125	(53.0)	49	(70.0)	
≥2	132	(43.1)	111	(47.0)	21	(30.0)	

Abbreviations: aCCI, age-adjusted Charlson comorbidity index; BMI, body mass index; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index.

response rate (ORR) and median OS.[26] Notably, only 16.4% of the study cohort in the reviewed literature were aged ≥70 years, suggesting that the number of older patients was insufficient in most clinical trial settings. Additionally, a prospective study by Prager et al[27] showed that older and younger patients with metastatic pancreatic cancer had comparable ORR, PFS, and OS, although fatigue and decreased appetite were more frequent in older patients. More importantly, 1 study by Trumper et al[12] analyzed 1080 patients with gastric cancer from 3 clinical trials and demonstrated that age was not an independent prognostic factor for OS. The ORR was not significantly different between the ≥70 and <70 year-old groups. These data validated this study's results that DCR, PFS, and OS were not substantially different between the old and young groups. This study's propensity score matching and subgroup analyses were consistent and showed no significant difference in OS between the old and young groups.

In terms of outcome prediction for patients with mGC treated with palliative chemotherapy, Yoshida et al[28] demonstrated that a better PS, a small number of metastatic sites, and macroscopically non-scirrhous type tumors are favorable factors for survival. Chau et al[29] proposed a prognostic index for mGC based on clinical trials conducted between 1992 and 2001. This prognostic index has been widely used with 4 independent risk factors of ECOG PS of ≥2, liver metastasis, peritoneal metastasis, and serum alkaline phosphatase level of ≥100 U/L. However, the index proposed by Chau et al was established using data from Western patients. Patients with esophageal cancer accounted for 27.3% of the study population. To overcome this limitation, Takahari et al[30] used data from a large prospective, randomized controlled study to generate another prognostic index for Japanese patients with advanced gastric cancer. In contrast to the prognostic model

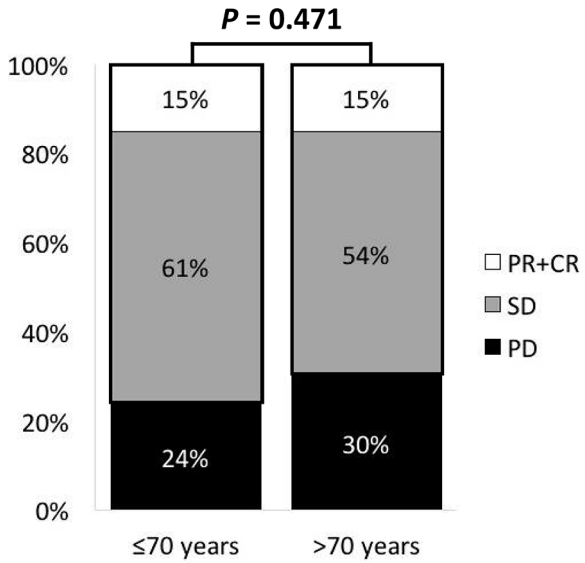

Figure 2. Treatment response comparison among older (>70 years of age) and younger patients (⩽70 years of age). CR indicates complete response; PD, progressive disease; PR, partial response; SD, stable disease.

established by Chau et al, the model established by Takahari et al comprised independent factors of ECOG PS of ⩾1, 2 or more metastatic sites, no prior gastrectomy, and elevated alkaline phosphatase levels. Furthermore, Sun et al[31] explored the prognostic significance of tumor markers and suggested that the elevated pre-chemotherapy CA19-9 level was a poor prognostic marker. These data supported this study's results that the ECOG PS of 2-4, 2 or more metastatic sites, a higher CA19-9 level, and undergoing palliative gastrectomy were independent prognostic factors for patients with mGC who received palliative chemotherapy. The role of palliative gastrectomy in mGC is controversial. Chemotherapy combined with surgery may provide a survival benefit for selected patients with mGC.[24,32,33]

NLR is a widely used biomarker of cancer-related inflammation. Basic research revealed that inflammatory cytokines are associated with tumor progression and adverse systemic effects.[34] This study's cohort indicated that high NLR was associated with poor outcomes in patients receiving palliative chemotherapy. Cho et al[35] demonstrated that pre-treatment NLR is a prognostic marker for survival outcomes in mGC. Although the prognostic impact of NLR in advanced gastric cancer was established in many studies, controversy exists regarding the optimal cut-off value. We determined 4.5 as the reasonable cut-off value because the median value in our cohort was 4.6, and previous studies had reported 4.5 as a meaningful cut-off value.[18] Besides, it was proposed that NLR positively correlates with age in a healthy population. However, the old and young groups had similar NLR in this study with mGC. More evidence is needed to confirm the ideal cut-off value and the difference in NLR between the old and young groups in advanced gastric cancer.

Not surprisingly, single-agent chemotherapy was more commonly administered in the old group than in the young group. Moreover, only 30.0% of the old group patients received second-line or later-line palliative chemotherapy compared with 47.0% of the young group. Many prospective studies have elucidated the efficacy of combination chemotherapy in advanced gastric cancer; however, conflicting results exist.[36-38] A meta-analysis by Wagner et al[39] demonstrated that combination chemotherapy provided a better therapeutic efficacy in patients with mGC than monotherapy (HR: 0.83; 95% CI: 0.94-0.93). Currently, a combination of platinum and fluoropyrimidine remains the standard of care for patients with mGC.[6,7] However, the univariate analysis in this study did not indicate that combination chemotherapy provided better OS than single-agent chemotherapy. The old and young groups had similar OS duration, suggesting that monotherapy could be a feasible treatment for older patients with mGC. This hypothesis was supported by a randomized phase III study, which showed that older patients with mGC treated with combination and single-agent chemotherapies had comparable OS.[40] After all, real-world patients are generally older and less fit than patients in clinical trials. The efficacy and safety must be carefully balanced.

Our data showed that the old group had less chemotherapy-related neutropenia than the young group. This may reflect that the clinical physician might modify the regimen or dose based on the patient's fitness. The current study further supports the potential application of a less-intensive regimen, such as monotherapy for older patients with mGC. The incidence of Grade 3-4 hematologic adverse events was not significantly different between the 2 groups. A pooled analysis of 3 clinical trials validated our results, which showed a comparable incidence of Grade 3-4 toxicity between the younger and older cohorts.[12] Based on these findings, older patients with mGC may benefit from palliative chemotherapy after careful assessment.

Our study revealed that patients in the young group were more likely to have poorly differentiated adenocarcinoma and signet-ring features. This result was consistent with the finding of Taghavi et al[41] that patients with signet-ring cell carcinoma were younger than those without it (61.9 vs 68.7 years; $P < .001$). This data consistency confirms the accuracy of our database.

Our study has some limitations. First, it had a retrospective study design with missing data. Second, treatment regimens were diverse, and chemotherapy regimens mainly depended on physicians' choices. Third, our study did not analyze some vital non-hematologic adverse events, such as diarrhea, nausea/vomiting, or quality of life. Fourth, the diagnosis of *H pylori* infection was only by Giemsa staining. Finally, a geriatric assessment was not recorded, and a chemotherapy toxicity predictive tool was not applied. Since previous studies have elaborated that geriatric assessment could improve the treatment course with less treatment-related toxicity,[42-44] future studies with prospective, randomized controlled study design, and comprehensive geriatric assessment are needed to evaluate the most optimal therapeutic strategy for older patients with mGC.

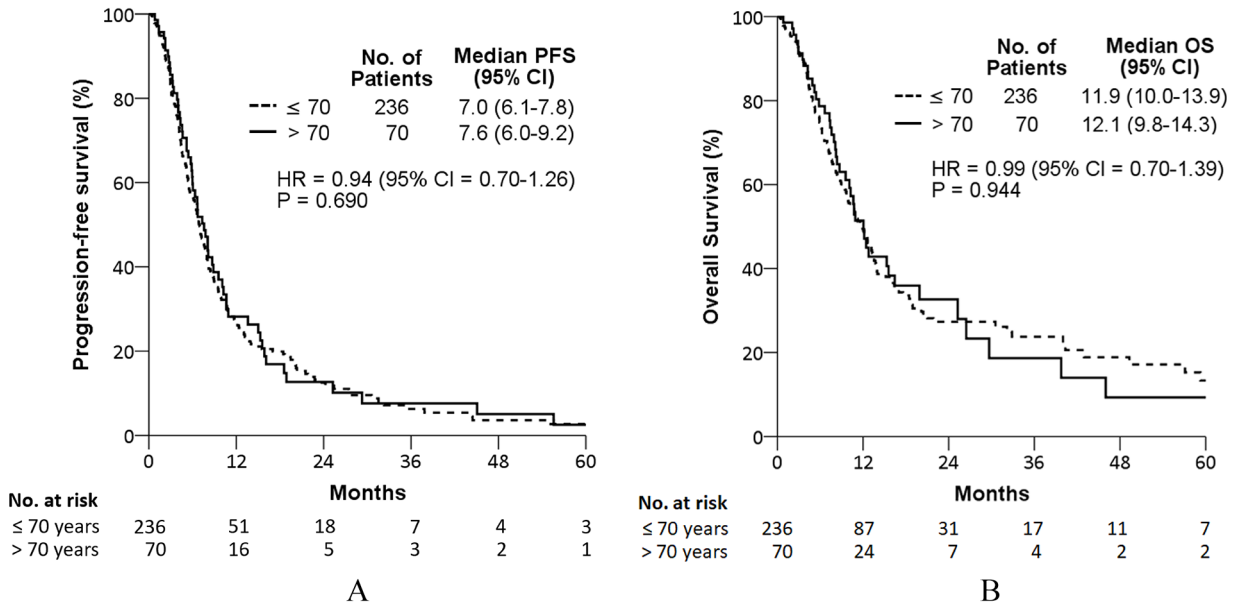

Figure 3. (A) PFS and (B) OS of patients receiving chemotherapy, and comparison among older (>70 years of age) and younger patients (⩽70 years of age). CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Table 3. Prognostic factors of patients who received chemotherapy.

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Age, years						
⩽70	Reference					
>70	0.99	(0.70-1.39)	.944			
Sex						
Male	Reference					
Female	1.22	(0.92-1.63)	.165			
BMI						
18.5-23.9	Reference					
<18.5	1.36	(0.90-2.06)	.140			
⩾24.0	0.80	(0.57-1.13)	.212			
ECOG performance status						
0-1	Reference			Reference		
2-4	2.05	(1.52-2.76)	<.001	1.63	(1.08-2.46)	.020
aCCI						
0-3	Reference					
⩾4	0.88	(0.60-1.29)	.526			
Primary site						
Gastroesophageal junction	Reference					
Cardia	1.12	(0.49-2.58)	.785			

(Continued)

Table 3. (Continued)

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
Fundus/body	1.14	(0.57-2.29)	.709			
Antrum	0.96	(0.47-1.95)	.914			
Pylorus	2.10	(0.70-6.29)	.184			
Entire	2.32	(0.71-7.55)	.161			
Anastomosis site	1.29	(0.54-3.07)	.570			
Burden of metastatic disease						
1	Reference			Reference		
⩾2	2.47	(1.85-3.30)	<.001	2.03	(1.37-2.98)	<.001
Histologic grade						
Grade 1-2	Reference			Reference		
Grade 3	1.64	(1.08-2.48)	.021	1.23	(0.73-2.07)	.438
Signet-ring feature						
No	Reference					
Yes	0.93	(0.69-1.26)	.655			
HER2 overexpression						
0, 1+, 2+	Reference					
3+	1.25	(0.76-2.04)	.385			
H pylori infection						
No	Reference			Reference		
Yes	1.54	(1.06-2.25)	.023	1.19	(0.77-1.83)	.443
CEA level ⩾ 5 U/mL						
No	Reference					
Yes	1.28	(0.95-1.72)	.105			
CA 19-9 level ⩾ 34 U/mL						
No	Reference			Reference		
Yes	1.75	(1.26-2.43)	.001	1.51	(1.02-2.24)	.038
NLR						
⩽4.5	Reference			Reference		
>4.5	2.00	(1.50-2.67)	<.001	2.00	(1.38-2.89)	<.001
PNI						
⩽40	Reference					
>40	0.86	(0.64-1.14)	.295			
Palliative gastrectomy						
No	Reference			Reference		
Yes	0.44	(0.33-0.59)	<.001	0.62	(0.41-0.93)	.021

(Continued)

Table 3. (Continued)

	UNIVARIATE ANALYSIS			MULTIVARIATE ANALYSIS		
	HR	(95% CI)	*P*	HR	(95% CI)	*P*
First-line chemotherapy						
Single agent	Reference					
Combination	0.80	(0.55-1.16)	.240			
Line of chemotherapy						
1	Reference					
⩾2	0.80	(0.60-1.07)	.129			

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; aCCI, age-adjusted Charlson comorbidity index; HER2, human epidermal growth factor receptor 2; CEA, carcinoembryonic antigen; CA 19-9, carbohydrate antigen 19-9; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutrition index; HR, hazard ratio; CI, confidence interval.

Table 4. Hematologic side effects of chemotherapy.

	ALL GRADES				GRADE 3-4				
	⩽70YEARS (N=236)		>70YEARS (N=70)		⩽70YEARS (N=236)		>70YEARS (N=70)		*P*
Leukopenia, n (%)	103	(43.6)	23	(32.9)	14	(5.9)	1	(1.4)	.205
Neutropenia, n (%)	77	(32.6)	13	(18.6)	25	(10.6)	7	(10.0)	1.000
Anemia, n (%)	175	(74.2)	52	(74.3)	57	(24.2)	14	(20.0)	.574
Thrombocytopenia, n (%)	130	(55.1)	38	(54.3)	27	(11.4)	4	(5.7)	.242
Febrile neutropenia, n (%)	8	(3.4)	2	(2.9)	8	(3.4)	2	(2.9)	1.000

Conclusions

In conclusion, older age alone might not be an obstacle to administering palliative chemotherapy to patients with mGC. Less intensive chemotherapy may be an alternative treatment for older and fragile patients. Further prospective, randomized, controlled studies are needed to validate these results.

Authors Contributions

P-WL and Y-HS performed the research. S-BC, C-WC, and H-CL designed the study. C-HL, T-CC, and C-YH analyzed the data. P-WL, C-LJT, and Y-HS wrote the article. All authors reviewed the results and approved the final version of the article.

Ethics Approval

The study was conducted according to the principles of the Declaration of Helsinki. The institutional review board of Taichung Veterans General Hospital approved the study and waived the requirement for informed consent because of its retrospective design (grant no. CE21334A).

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Supplemental Material

Supplemental material for this article is available online.

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