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ORIGINAL ARTICLE

Efficacy and safety of chemotherapy in young patients with advanced gastroesophageal adenocarcinoma: data from the Spanish AGAMENON-SEOM registry

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Abstract

Background Gastroesophageal adenocarcinoma in young adults (GCYA) counts for 10–15% of diagnoses. Previous studies have mainly focused on surgical outcomes in patients with resectable tumors; however, systemic therapy for advanced GCYA remains under-evaluated. This study aims to assess the efficacy-related outcomes and safety of first-line chemotherapy (CT) in younger versus older patients with advanced gastroesophageal adenocarcinoma.

Methods Patients with advanced gastroesophageal adenocarcinoma from the AGAMENON-SEOM registry treated with first-line polychemotherapy between January 2008 and October 2022 were included. We compared clinicopathological features, therapies received, efficacy-related outcomes, and toxicity between individuals aged < and ≥ 45 years.

Results Out of 3386 patients, 263 (7.8%) were < 45 years. Young patients exhibited a higher proportion of females affected, lower ECOG-PS ≥ 2, fewer comorbidities, and more aggressive disease-related features, such as higher proportion of diffuse subtype, signet-ring cells, plastic linitis, grade 3, peritoneal metastases and metastatic disease at diagnosis. They received more triple-agent combinations and underwent more surgeries in metastatic setting. No significant differences were observed between groups in overall response rate (53.1% vs. 52.3% in < and ≥ 45 years, respectively, $p = 0.579$), progression-free survival (6.1 vs. 6.83 months, $p = 0.158$) and overall survival (11.07 vs. 10.81 months, $p = 0.82$), even after adjusting for potential confounding factors. Grade 3–4 adverse events were comparable in both groups, although toxicity leading to treatment discontinuation was more frequent in older patients.

Conclusions In the AGAMENON-SEOM registry, younger patients with GCYA exhibited more aggressive clinicopathological features, and despite receiving more aggressive treatments, similar efficacy outcomes and toxicity profiles were achieved compared to their older counterparts.

Miniabstract In the AGAMENON-SEOM registry, GEAC in < 45 years showed more aggressive clinicopathological features and, although treated with more intense first-line CT regimens, similar efficacy outcomes and toxicity were achieved compared to older patients.

Keywords Gastroesophageal adenocarcinoma · Young patients · First-line chemotherapy · Efficacy-related outcomes · Toxicity

Introduction

Gastroesophageal adenocarcinoma (GEAC) ranks as the fifth most diagnosed malignancy and the fourth leading cause of cancer-related death globally [1]. They are generally aggressive tumors with limited treatment options and

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poor prognosis, with 5-year survival rates ranging from 76% to 5.7% for stage I and IV, respectively [2]. Although GEAC primarily manifests in individuals aged 50–70 years, 5–10% of patients are diagnosed at a younger age [3–7]. It is worth noting that, despite global GEAC incidence and mortality rates have declined worldwide, a stable or even slightly increasing trend has been reported among young adults in both Eastern and Western populations [4, 5, 8].

Compared to older patients, GEAC in young adults (GCYA) possesses distinctive clinicopathological attributes, such as female dominance, family history, location in the upper third region, poor prognosis histopathological factors (poor differentiation, diffuse subtype, signet ring cells), more advanced stage at diagnosis, fewer comorbidities, and improved suitability for treatment [5–35]. Evidence regarding the prognosis of this group is conflicting. While some authors report worse survival compared to older cohorts, particularly in the metastatic setting [11, 13, 14, 18, 20, 24, 25], more recent studies find equivalent [3, 7, 16, 19, 21, 23, 24, 26–32, 35–37] or even improved outcomes [9, 33, 34].

Therapeutic options for advanced GEAC have not been stratified by age. A platinum-fluoropyrimidine chemotherapy (CT) doublet, with the addition of trastuzumab for HER2-overexpressing tumors has been long considered the standard first-line therapy [38]. More recently, nivolumab [39] and pembrolizumab [40, 41] in combination with CT have shown to improve survival in HER2-negative GEAC, while initial results from the KEYNOTE-811 have found significantly higher objective response rates (ORR) with the addition of pembrolizumab to CT and trastuzumab in HER2-positive disease [42]. The median age of patients included in these studies ranges from 60 to 65 years, with up to 50% of patients above 65 years, thereby featuring limited representation of younger patients. Regarding the role of surgery, primary tumor resection in patients diagnosed with metastatic cancer appears not to clearly improve survival [43]. Although surgery for metastases has been suggested to be beneficial in specific oligometastatic patients who respond to induction treatment in the phase II AIO-FLOT3 study [44], there is still a requirement for additional prospective assessment.

Most of the available data to date in relation to potential differences in efficacy of standard therapies between young and older patients come from small, mostly unicentric, retrospective studies [3, 7, 9–13, 18, 23, 25] and some meta-analyses [27, 34], which have mainly focused on surgically treated patients [7, 13, 15–17, 19, 29, 31, 36, 37] or included heterogeneous populations through all stages of disease [4, 9, 12, 14, 18, 20–28, 30, 32–35]. However, systemic CT for the treatment of advanced GCYA has only been assessed in two Japanese studies so far [10, 11].

This real-world analysis, based on the Spanish AGAMENON-SEOM registry, aims to compare clinicopathological features, treatment regimens, efficacy-related outcomes, and safety profiles between advanced GCYA and older patient subgroups undergoing first-line polychemotherapy. This study is pioneering in its evaluation of standard systemic CT use within a Caucasian advanced GCYA cohort, thus addressing a notable research gap.

Methods

Study population and design

Patient data were extracted from the AGAMENON-SEOM registry of GEAC, with contributions from 42 Spanish university hospitals. The main characteristics of the registry, methodologies, and data collection criteria have been detailed elsewhere [45, 46]. AGAMENON-SEOM, an observational registry supported by SEOM's Clinical Practice and Results Evaluation section, examines diagnostic-therapeutic practices within participating centers. Data was systematically collected through an electronic case report platform (http://www.agamenonstudy.com) containing filters and a system of queries to ensure data reliability.

Eligibility criteria included adults (≥ 18 years) with histologically confirmed locally advanced unresectable or metastatic gastric, gastroesophageal junction (GEJ), or distal esophageal adenocarcinoma treated with at least one cycle of first line polychemotherapy (≥ 2 drugs) between January 2008 and October 2022. Exclusion criteria included less than 3 months of follow-up, unless death occurred during this period, less than 6 months since the conclusion of any adjuvant or neoadjuvant therapy, synchronous cancers, treatment with single-agent CT, or participation in a clinical trial. This study includes HER2-positive patients treated with trastuzumab since the publication of the TOGA study in 2010 [47]. As immunotherapy did not receive public funding in Spain until August 2023, the few patients who received these drugs during the study period were participants in clinical trials and thus excluded from the analysis.

Three distinct populations were analyzed for the different endpoints: clinicopathological characteristics and CT schedules, survival and safety, and ORR assessment (Fig. 1). Survival analysis required to have survival data available, while tumor response analysis demanded measurable disease at baseline and at least one objective evaluation around 3 months later according to RECIST version 1.1 criteria.

Ethical approval was obtained from the Research Ethics Committees of all participating centers and living patients at the time of data collection provided signed informed consent.

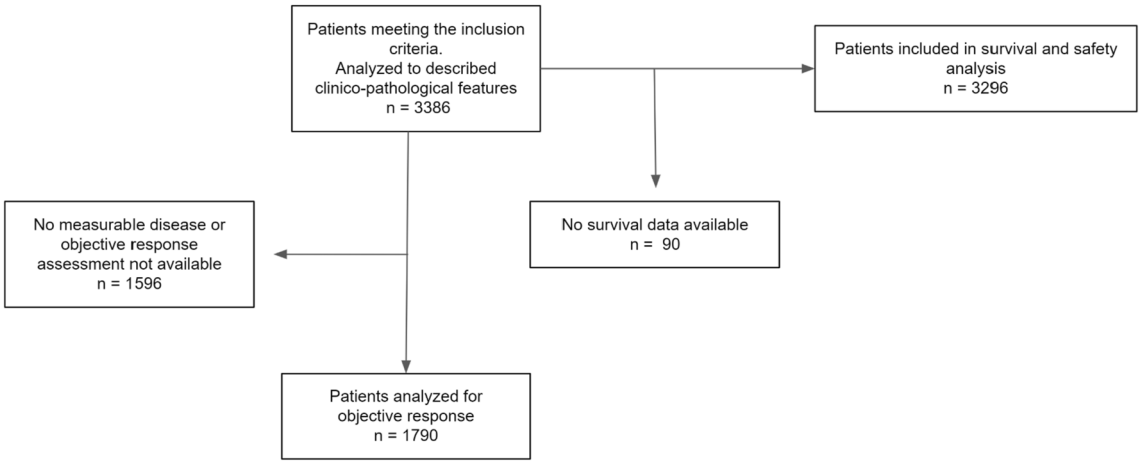

Fig. 1 Flow chart. Selection process in our study

Variables and outcomes

Epidemiological, histopathological, clinical, and therapeutic variables were obtained from patient records. "Young patient" was defined as being under 45 years old at advanced GEAC diagnosis.

Primary outcomes encompassed overall survival (OS) and progression-free survival (PFS), calculated from first-line CT initiation to all-cause mortality or progression, respectively, and censoring patients without any event at the last follow-up. Secondary outcomes included ORR per RECIST version 1.1 and toxicity classified according to Common Terminology Criteria of Adverse Events (CTCAE) version 4.0.

CT schedules, dose intensity, and number of cycles were documented based on real-life clinical practice and determined at the investigator's discretion. To compare CT schedules, five strata were defined: cisplatin-fluoropyrimidine doublet, oxaliplatin-fluoropyrimidine doublet, irinotecan-based schedules, anthracycline-based regimens, and docetaxel-based triple-agent therapy. Cumulative dose was defined as the total administered dose in mg/m^2. Dose intensity was defined as the amount of drug administered per unit of time, expressed as milligrams per square meter (mg/m^2) weekly.

Clinicopathological variables with known prognostic relevance in GEAC, as documented in previous studies, were collected as potential confounding factors: albumin and hemoglobin below normal limits, lactate dehydrogenase (LDH) or alkaline phosphatase (ALP) above normal limits, ascites, bone, lung, or peritoneal metastases, histological grade 2–3, Eastern Cooperative Oncology Group-performance status (ECOG-PS) ≥ 2, stage IV at diagnosis, number of metastatic sites ≥ 3, diffuse histotype, presence of signet ring cells, neutrophil-to-lymphocyte ratio (NLR) > 4, HER-2 overexpression, primary tumor or metastasis surgery, and prior perioperative treatment.

Statistical analysis

Standard descriptive statistics were used, including absolute and relative frequencies, means, and medians. Clinicopathological characteristics, CT regimen distributions, best response frequencies, and toxicity grades were compared between age groups using the Chi-square test for qualitative variables and *T*-student (if normal distribution) or Mann Whitney (if not normal distribution) for quantitative variables. Normal distribution was examined via the Kolmogorov–Smirnov test. Significance was set at $p < 0.05$ with two-tailed p values and 95% confidence intervals (CIs) where applicable.

OS and PFS probabilities were estimated using the Kaplan–Meier method and compared by the log-rank test. The effect of potential confounding factors on survival was initially evaluated in univariate screening, selecting variables with $p < 0.10$ for inclusion in the multivariable Cox proportional hazards model (forward selection). Age was included in all the analyses due to its relevance in our study. Variables with over 30% missing values were excluded. Statistical analysis was performed using SAS 9.3 (SAS Institute, Cary, NC, USA).

Results

Patients, demographic and clinicopathological features

At the time of data cutoff (October 22), the registry contained 3386 patients, 263 (7.8%) of whom were < 45 years old. Figure 1 illustrates the recruitment process.

Baseline characteristics by age group are presented in Table 1. Differences between younger and older subsets

include a higher proportion of females (41.1% vs. 28.4%, $p < 0.001$), lower ECOG-PS ≥ 2 cases (10.6% vs. 14.5%, $p = 0.013$), a higher frequency of low body mass index (12.9% vs. 5.8%, $p < 0.001$), and fewer patients with at least two comorbidities (3.1% vs. 20.9%, $p < 0.001$) in < 45 years. Chronic heart disease, chronic vascular disease, and diabetes mellitus were less common in younger patients.

Young adults exhibited more aggressive disease-related features, such as metastatic or unresectable disease at diagnosis (vs. recurrent disease) (87.1% vs. 79.5, $p = 0.003$), Lauren diffuse subtype (61% vs. 39.2%, $p < 0.001$), signet ring cells (54.3% vs. 33.5%, $p < 0.001$), plastic linitis (22.1 vs. 10.3%, $p < 0.001$), grade 3 tumors (56.9% vs. 51.5%, $p = 0.001$), peritoneal disease (55% vs. 43.6%, $p < 0.001$), and ascites (34% vs. 21.4%, $p < 0.001$) compared to older adults. Older adults showed lower albumin and higher carcinoembryonic antigen (CEA) levels. No age-based differences were observed in HER-2 overexpression prevalence, primary tumor site (distal esophagus, GEJ, or gastric), or the number of metastatic organs.

Use of chemotherapy and other therapies according to patients' age

Table 2 summarizes CT regimens by age. Key points include increased use of triple-agent CT (43.5% vs. 24.8%, $p < 0.001$), both docetaxel (20.6% vs. 9.3%, $p < 0.001$) or anthracycline-containing schedules (25.9% vs. 17.3%, $p < 0.001$), and reduced use of oxaliplatin-containing CT (30.2% vs. 46.1%, $p < 0.001$) in younger patients. Most common regimens for younger patients were EOX (19%), FOLFOX-6 (16%), and CAPOX (12.5%), while older patients predominantly received CAPOX (21.8%) and FOLFOX-6 (18.7%). No age-based differences were noted in cisplatin-based regimens (17.5% vs. 19.5% for < 45 and ≥ 45 years, respectively) or first-line trastuzumab (20.6% vs. 19.9%, respectively).

Minor differences were found in the number of courses or median CT duration based on age (Supplementary Table 1). Notably, younger patients treated with CAPOX received higher mean total and per-cycle oxaliplatin doses, and those treated with XP higher mean total cisplatin doses. In contrast, older individuals treated with ECF or ECX schedules received significantly higher mean total cisplatin doses, along with higher total and per-cycle capecitabine doses with XP or CAPOX regimens. Primary reasons for first-line CT discontinuation in both groups were disease progression or completion of planned therapy.

Second-line CT was more commonly administered to patients < 45 years than to their older counterparts (64.9%

Table 1 Baseline characteristics

Baseline characteristic	< 45 years n = 263 N (%)	≥ 45 years n = 3123 N (%)	*p*-value
Age, median (interquartile range)	40.02 (36.02–42.67)	65.4 (57.2–72.2)	–
Sex, female	101 (41.1)	888 (28.4)	< 0.001
BMI (kg/m²)			< 0.001
< 18.5	34 (12.9)	182 (5.8)	
18.5–24.9	159 (60.5)	1578 (50.5)	
> 25	70 (26.6)	1363 (43.6)	
ECOG-PS			0.013
0	81 (30.8)	729 (23.3)	
1	154 (58.6)	1940 (62.1)	
≥ 2	28 (10.6)	454 (14.5)	
Number of comorbidities			
No	220 (84)	1662 (53.6)	< 0.001
1	34 (13)	791 (25.5)	
≥ 2	8 (3.1)	647 (20.9)	
Comorbidities			
Chronic heart disease	7 (2.7)	378 (12.2)	< 0.001
Chronic renal failure	1 (0.4)	67 (2.2)	–
Chronic vascular disease	4 (1.5)	294 (9.5)	< 0.001
Diabetes mellitus	5 (1.9)	516 (16.6)	< 0.001
Chronic liver disease	2 (0.8)	57 (1.8)	-
Thromboembolic disease	6 (2.3)	177 (5.7)	0.015
Chronic lung disease	2 (0.8)	223 (7.2)	–
Dementia	0 (0)	11(0.4)	–
AIDs	1 (0.4)	17 (0.5)	–
Other	23 (8.8)	587 (18.9)	< 0.001
Complication at diagnosis	20 (7.6)	245 (7.9)	1
TNM stage at first diagnosis			0.004
I-III	40 (15.2)	709 (22.9)	
IV	223 (84.8)	2393 (77.1)	
De novo metastatic or unresectable (vs. recurrent disease)	229 (87.1)	2482 (79.5)	0.003
Primary tumor site			0.57
Esophagus	27 (10.4)	271 (8.8)	
GEJ	38 (14.7)	415 (13.5)	
Stomach	194 (74.9)	2380 (77.6)	
Plastic linitis	58 (22.1)	321 (10.3)	< 0.001
Histological grade			0.001
G1	10 (4.9)	324 (14)	
G2	79 (38.3)	798 (34.5)	
G3	117 (56.9)	1193 (51.5)	
Not available	57 (21.7)	808 (25.8)	
Lauren classification			< 0.001
Intestinal	72 (35.1)	1317 (54.4)	
Diffuse	125 (61)	948 (39.2)	
Mixed	8 (3.9)	154 (6.4)	
Not available	58 (22)	704 (22.5)	

Table 1 (continued)

Baseline characteristic	< 45 years n = 263 N (%)	≥ 45 years n = 3123 N (%)	*p*-value
Signet ring cells	113 (54.3)	855 (33.5)	< 0.001
HER-2 overexpression			0.888
No	168 (73.4)	1992 (74.1)	
Yes (3+)	45 (19.7)	497 (18.5)	
Yes (2+ and FISH+)	16 (7)	201 (7.5)	
Not available	34 (12.9)	433 (13.9)	
Number of metastatic sites			
< 3	190 (72.5)	2311 (74.4)	0.508
≥ 3	72 (27.5)	794 (25.6)	
Metastases sites			
Liver	82 (31.3)	1155 (37.2)	0.602
Lung	32 (12.2)	447 (14.4)	0.358
Non-regional lymph nodes	127 (48.5)	1428 (46)	0.44
Peritoneal	144 (55)	1355 (43.6)	< 0.001
Ascites	89 (34)	665 (21.4)	< 0.001
Bone	32 (12.2)	309 (10)	0.4
Other sites	64 (24.4)	395 (12.7)	< 0.001
Laboratory findings			
Albumin < lower limit of normal	41 (18.3)	720 (26.2)	0.009
Neutrophil–lymphocyte ratio > 4	91 (36.1)	1108 (36.6)	0.94
CEA median (interquartile range)	3 (1–19)	4 (2–21)	0.004
Hemoglobin < lower limit of normal	168 (65.4)	2063 (67.2)	0.535
LDH > higher limit of normal	55 (26.2)	789 (31.6)	0.121
ALP > higher limit of normal	79 (31.7)	921 (31.1)	0.831

In the Table, percentages refer to proportions of the columns. N, sample size; AIDs, Acquired immune deficiency syndrome; ALP, alkaline phosphatase; BMI, body mass index; CEA, carcinoembryonic antigen; ECOG-PS, Eastern Cooperative Oncology Group-performance status; GEJ, Gastroesophageal junction; FISH, Fluorescent in situ hybridization; LDH, lactate dehydrogenase

vs. 53.1%, $p = 0.001$). Regarding surgical interventions, 277 patients with advanced disease at diagnosis underwent primary tumor resection, which was more common in the younger subgroup (17.9% vs. 9.9%, $p < 0.001$). These surgeries were less frequent in distal esophagus or GEJ tumors than in gastric location (6.5% vs. 12.8%, $p < 0.001$) for the entire series, but no significant differences were found in young patients (17.9% vs. 18.3%, $p = 0.94$). Surgery for metastases was performed in 154 cases and was also more frequent in < 45 years (14% vs. 3.9%, $p < 0.001$) (Table 2).

Table 2 Most common chemotherapy schedules and other therapies according to participants' age

Chemotherapy schedules	< 45 years n = 263 N (%)	≥ 45 years n = 3123 N (%)	*p*
EOX	50 (19)	372 (11.9)	0.002
mFOLFOX-6	42 (16)	583 (18.7)	0.283
CAPOX	33 (12.5)	682 (21.8)	< 0.001
XP	17 (10.3)	402 (12.5)	0.247
FP 3w	18 (6.8)	173 (5.5)	0.404
DCF 3w	15 (5.7)	65 (2.1)	0.001
FLOT	13 (4.9)	40 (1.3)	< 0.001
ECX	12 (4.6)	104 (3.3)	0.291
DCX	10 (3.8)	60 (1.9)	0.066
ECF	5 (1.9)	46 (1.5)	0.595
First-line Chemotherapy regimens			
Triplet combination	114 (43.5)	765 (24.8)	< 0.001
Oxaliplatin-based doublets	79 (30.2)	1422 (46.1)	< 0.001
Anthracycline-based	68 (25.9)	532 (17.3)	< 0.001
Cisplatin-based	46 (17.6)	609 (19.8)	0.418
Docetaxel-based	54 (20.6)	288 (9.3)	< 0.001
Irinotecan-based	6 (2.3)	52 (1.7)	–
Other	9 (3.4)	180 (5.8)	–
First-line trastuzumab	54 (20.6)	615 (19.9)	0.96
Surgery of metastasis	36 (14)	118 (3.9)	< 0.001
Primary tumor surgery in metastatic disease at diagnosis	40 (17.9)	237 (9.9)	< 0.001
Use of G-CSF			
Yes/No	56 (21.5)	486 (15.8)	0.022
Secondary prophylaxis (vs. primary prophylaxis)	36 (13.8)	287 (9.3)	0.039
Second-line chemotherapy	159 (64.9)	1547 (53.1)	0.001

In the Table, percentages refer to proportions of the columns. G-CSF, granulocyte-colony stimulating factor

Treatment outcomes based on age

Among 3296 individuals eligible for survival analysis, there were 2871 death events (87.1%), 220 (85.6%) in the younger group and 2651 (87.2%) in the older group. After a median follow-up of 10.3 months (interquartile range (IQR) 5.39–17.49), median OS for the entire cohort was 10.84 months (95% CI 10.45–11.24). No differences were observed by age, with a median OS of 11.07 months (95% CI 9.47–12.68) for patients < 45 and 10.81 months (95% CI 10.4–11.22) for those ≥ 45 ($p = 0.825$) (Fig. 2a). The 12-month survival rate was 44.41% (95% CI 38.49–51.24) for subjects < 45 and 44.39% (95% CI 42.61–46.25) for those ≥ 45 years.

Similarly, 2595 progressions to first-line treatment (83.3%) were recorded, 216 (87.4%) in < 45 years and 2379

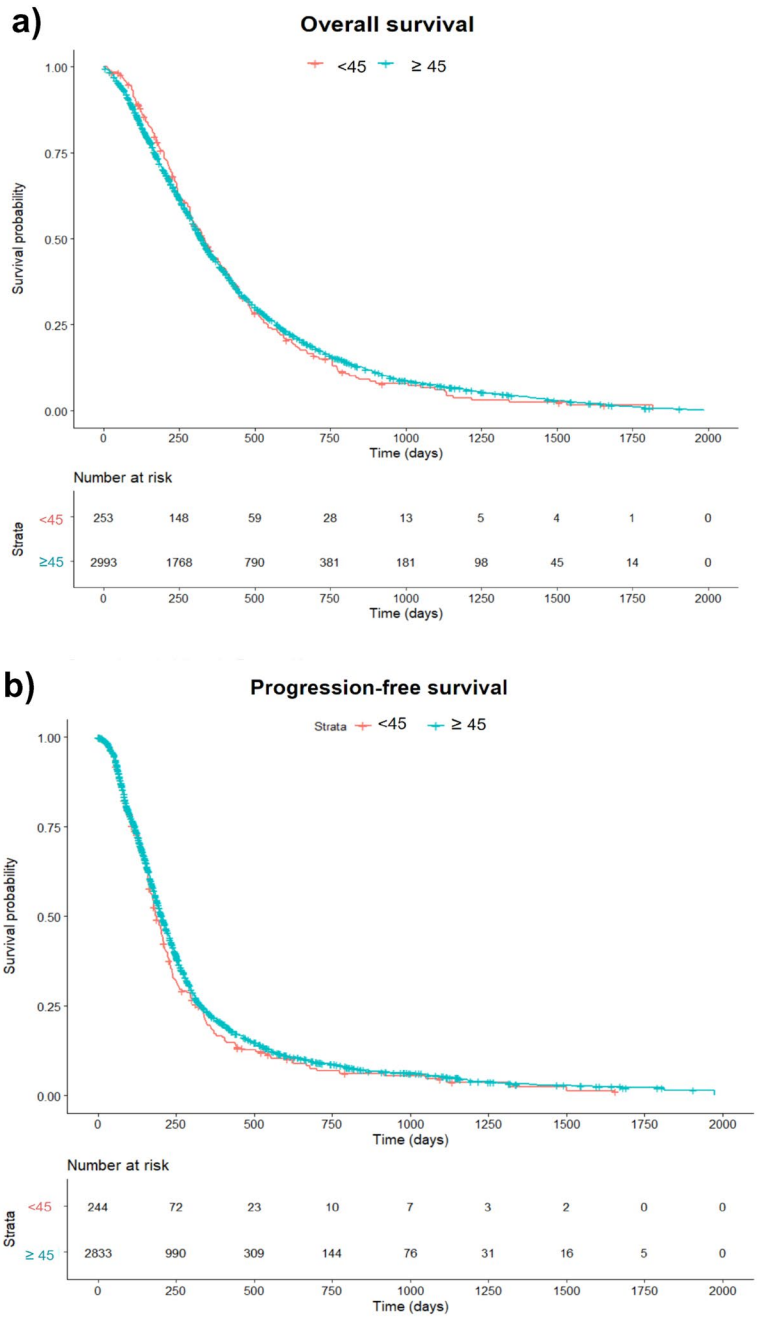

Fig. 2 Kaplan–Meier curves for OS (**a**) and PFS (**b**) according to age

(82.9%) in ≥ 45 years. Median PFS for the entire series was 6.80 months (95% CI 6.57–7.02), without significant differences based on age. Young adults had a median PFS of 6.10 months (95% CI 5.57–6.79) compared to 6.83 months (95% CI 6.59–7.08) in ≥ 45 ($p = 0.158$) (Fig. 2b).

Univariate (Table 3a) and multivariate (Table 3b) Cox-regression analyses were performed in the entire study population. After adjusting for potential prognostic variables, although a trend towards a better prognosis was observed in < 45, age was confirmed not to be an independent prognostic factor for either OS (HR = 0.80, 95% CI 0.64–1.01, $p = 0.06$) or PFS (HR = 0.83, 95% CI 0.67–1.04, $p = 0.12$). Among various factors, metastatic disease at diagnosis (vs. recurrent disease) and the absence of primary tumors or metastasis surgeries are identified as unfavorable prognostic markers for survival. When outcomes were examined by age and initial tumor stage, patients ≥ 45 with recurrent disease showed notably better OS and PFS than those with primary metastatic disease, regardless of age. However, differences in relation to < 45 with recurrent disease were not statistically significant (Supplementary Fig. 1a, b).

Table 3 Univariate (a) and multivariate (final step, (b)) Cox proportional hazard regression analysis for overall survival and progression-free survival in overall population

(a) Univariate

	Overall survival		Progression-free survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age (< 45 vs. ≥ 45)	0.95 (0.83–1.09)	0.5	1.03 (0.90–1.18)	0.61
Sex, female	1.02 (0.94–1.10)	0.61	1.009 (0.92–1.097)	0.84
ECOG-PS, ≥ 2 vs. 0–1	2.02 (1.82–2.24)	< 0.001	1.51 (1.34–1.69)	< 0.001
Ascites	1.52 (1.4–1.66)	< 0.001	1.39 (1.27–1.52)	< 0.001
Bone metastases	1.508 (1.33–1.69)	< 0.001	1.45 (1.28–1.65)	< 0.001
Peritoneal metastases	1.26 (1.17–1.35)	< 0.001	1.14 (1.05–1.23)	0.001
Number of metastatic sites, ≥ 3	1.42 (1.31–1.55)	< 0.001	1.36 (1.25–1.49)	0.001
Albumin, < low limit normal	1.46 (1.34 -1.59)	< 0.001	1.29 (1.17–1.42)	< 0.001
Hemoglobin, < low limit normal	1.15 (1.06–1.24)	0.001	1.14 (1.05–1.23)	0.002
LDH, > upper limit normal	1.35 (1.23–1.472)	< 0.001	1.23 (1.12–1.35)	< 0.001
Stage at diagnosis, IV vs. I-III	1.14 (1.04–1.24)	0.004	1.09 (0.99–1.19)	0.06
Resection surgery of primary tumor in IV stage	0.60 (0.55–0.65)	< 0.001	0.64 (0.58–0.70)	< 0.001
Metastasis surgery	0.35 (0.28–0.42)	< 0.001	0.38 (0.31–0.46)	< 0.001
Lauren classification, diffuse vs. intestinal	1.33 (1.23–1.45)	< 0.001	1.22 (1.12–1.34)	< 0.001
Signet ring cells	1.3 (1.19–1.41)	< 0.001	1.22 (1.11–1.32)	< 0.001
Histological grade (2–3 vs. 1)	1.46 (1.28–1.66)	< 0.001	1.41 (1.23–1.62)	< 0.001
HER2 overexpression (IHQ 3 + / IHC 2 + and FISH +)	0.73 (0.67–0.8)	< 0.001	0.75 (0.69–0.83)	0.001
NLR > 4	1.54 (1.43–1.67)	< 0.001	1.35 1.24–1.46)	< 0.001
Chemotherapy schedule (triplets vs. doublets)	0.97 (0.90–1.06)	0.58	1.03 (0.94–1.12)	0.46
Tumor location (GEJ-distal esophagus vs. gastric)	0.98 (0.91–1.06)	0.73	0.96 (0.89–1.04)	0.4

(b) Multivariate (final step)

	Overall survival		Progression free survival	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Age, < 45 vs. ≥ 45	0.80 (0.64- 1.01)	0.06	0.83 (0.67–1.04)	0.12
Albumin < low limit of normal	1.20 (1.04–1.39)	0.01	–	–
Ascites	1.35 (1.17–1.560)	< 0.001	1.22 (1.05–1.41)	0.007
Bone metastases	1.31 (1.09–1.58)	0.004	1.37 (1.14- 1.65)	0.001
ECOG-PS, ≥ 2 vs. 0–1	(1.38–1.24–1.53)	< 0.001	1.17 (1.05–1.30)	0.004
Histological grade, 2–3 vs. 1	1.12 (1.03–1.2)	0.007	1–11 (1.02–1.21)	0.016
Stage at diagnosis, I-III vs. IV	0.69 (0.56–0.86)	0.001	–	–
Number of metastatic sites, ≥ 3	1.17 (1.02–1.34)	0.019	–	–
NLR, > 4	1.2 (1.11–1.43)	< 0.001	1.19 (1.05–1.35)	0.006
HER2 overexpression (IHC 3+ /IHQ 2+ and FISH+)	0.71 (0.61–0.82)	< 0.001	0.71 (0.61–0.82)	< 0.001
LDH, > upper limit normal	1.32 (1.64–1.51)	< 0.001	1.25 (1.10–1.42)	0.001
Resection surgery of primary tumor in IV stage	0.63 (0.52–0.77)	< 0.001	0.66 (0.54–0.80)	< 0.001
Metastasis surgery	0.43 (0.32–0.59)	< 0.001	0.49 (0.37–0.65)	< 0.001

(a) HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; IHC, immunohistochemistry; FISH, Fluorescent in situ hybridization; GEJ, gastroesophageal junction; NLR, neutrophil-to-lymphocyte ratio

(b) HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group-performance status; IHC, immunohistochemistry; FISH, Fluorescent in situ hybridization; NLR, neutrophil-to-lymphocyte ratio

The same Cox analyses were conducted in the younger subgroup (Supplementary Table 2a, b). Independent predictors of poorer OS included bone metastases, HER2-negative status, and the absence of metastasis resection. These factors, along with an NLR > 4, were associated with worse PFS. In relation to survival according to different treatment strategies in < 45 years, we did not find differences in terms of OS (HR = 0.99, 95% CI 0.76–1.28,

$p = 0.94$) or PFS (HR = 0.1, 95% CI 0.77–1.31, $p = 0.94$) according to triplet vs. doublet CT use (Supplementary Table 2a and Supplementary Fig. 2a, b). In contrast, as for the overall population, metastasis surgery significantly resulted in better outcomes for both OS (HR = 0.21, 95% CI 0.11–0.36, $p < 0.001$) and PFS (HR = 0.38, 95% CI 0.22–0.66, $p < 0.001$) in young patients. Primary tumor resection in patients diagnosed with primary metastatic disease significantly improved OS (HR = 0.43, 95% CI 0.32–0.58, $p < 0.001$) and PFS (HR = 0.54, 95% CI 0.39–0.74, $p < 0.001$) in univariate analysis.

No significant PFS or OS differences were identified based on the primary tumor location (gastric vs. esophageal-GEJ), either in the overall population (Table 3a) and specifically in younger patients (Supplementary Table 2a).

Among 1790 patients evaluable for response, there were no significant differences in ORR (53.1% vs. 52.3% in < 45 and ≥ 45 years, respectively), or clinical benefit rate (CBR) (82.3% vs. 80.7%, respectively) based on age ($p = 0.579$) (Table 4; Supplementary Fig. 3). In < 45, triple-agent CT slightly increased ORR and complete responses (Supplementary Fig. 2c), but differences over doublet regimens were not statistically significant.

Safety of chemotherapy based on age

Table 5 details prevalent adverse events (AEs) by age and specific CT regimens, while Supplementary Table 3 analyzes adverse effects by age only. Hematological toxicity analysis found any grade anemia to be more common in younger patients, especially with cisplatin-fluoropyrimidine doublets (78% vs. 63%). Conversely, grade ≥ 3 anemia was more frequent in older patients receiving anthracycline-based triplets. There were no significant age-related differences in neutropenia or thrombocytopenia rates, except for a higher prevalence of neutropenia and febrile neutropenia in younger patients treated with non-platinum-fluoropyrimidine doublets (other regimens) (63.3% vs. 41.3%).

Regarding non-hematological AEs, younger patients treated with anthracycline-based triplets had increased rates of nausea (65.8% vs. 52.4%) and vomiting (49.3% vs. 31.9%). Alopecia was more frequent in < 45 receiving oxaliplatin-fluoropyrimidine doublets (15.1% vs. 8.9%) and other regimens (56.7% vs. 29.3%). Neuropathy was generally more common in older patients, but grade ≥ 3 neuropathy was particularly evident in younger individuals receiving docetaxel triplets (13.8% vs. 3.5%). Aspartate aminotransferase (AST) elevation was more frequent in < 45, particularly in those treated with oxaliplatin-fluoropyrimidine doublets (30.1% vs. 15.1% for any grade, 4.3% vs. 1% for grade ≥ 3). A higher rate of grade ≥ 3 venous thromboembolism (VTE) was observed in younger patients treated with cisplatin-fluoropyrimidine doublets (18% vs. 5.7%).

Comparing toxicity related to triple- versus double-agent CT in younger patients, grade ≥ 3 neutropenia was more commonly observed in patients treated with anthracycline-based triplets, and grade ≥ 3 hand-foot syndrome and neuropathy in those treated with docetaxel-containing triplets compared to doublet CT. Triple-agent CT was also associated with higher rates of any grade alopecia and anthracycline-based triplets with toxicity-related admissions.

Rates of hospitalization (22.1% in both groups, $p = 1$) or death (0.8% vs. 0.6% in younger vs. older patients) due to toxicity were similar between age groups. Toxicity more often led to CT discontinuation in older individuals, particularly in those treated with CAPOX (26.7% vs. 9.7%, $p = 0.03$), EOX (21.3% vs. 6.1%, $p = 0.011$), and any anthracycline regimen (22.2% vs. 10.4%, $p = 0.025$) (Supplementary Table 1).

Discussion

In this study we have used real-world data from the national AGAMENON-SEOM registry of advanced GEAC to investigate the clinicopathological characteristics, efficacy outcomes and treatment-related toxicity associated with standard front-line CT in younger compared to older patients. The motivation for this research arises from the rising incidence of various cancers, including GEAC, among young adults over the past decade, as well as a growing body of evidence suggesting that GCYA is molecularly distinct from tumors in older age groups, indicating potential differences in etiology and emphasizing the need for tailored therapeutic approaches [5, 48, 49]. Despite advances in understanding GCYA, these patients are often grouped together with children and older adults in epidemiologic studies, masking critical age-related differences [48]. Additionally, there is a significant research gap due to the limited representation of young adults in pivotal studies of advanced GEAC, which predominantly focus on older populations with median ages around 60–65 years [39–42, 50–52], as well as lack of real-world clinical data on this population. In this scenario, our analysis stands as a pioneering effort to address this knowledge gap, as it is, to the best of or knowledge, the first comprehensive study of a large, homogenous, Caucasian cohort of advanced GEAC patients eligible for first-line combination chemotherapy, thus aiming to shed light on this understudied population.

It is worth noting the difficulty in defining GCYA, as various criteria have been proposed, such a diagnosis before 40 in some studies [3, 5, 10, 11, 15–17, 19, 21, 26, 31] or before 45 in others [18, 23, 24, 29, 32, 34, 36]. Alternative age thresholds of < 35 [12, 14, 20, 22] or < 50 [28, 33, 36] have also been suggested. It's important to recognize that age is best understood as a continuous variable, making any fixed age limit somewhat arbitrary rather than definitive. In our

Table 4 Evaluation of tumor response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) criteria based on age

ORR	< 45 years n = 147 N (%)	≥ 45 years n = 1643 N (%)	*p*
Complete response	6 (4.1)	38 (2.3)	0.579
Partial response	72 (49)	822 (50)	
Stable disease	43 (29.3)	466 (28.4)	
Progressive disease	26 (17.7)	317 (19.3)	

Analysis conducted in the population suitable for tumor response analysis (n = 1790)

study, the age cutoff was set at 45 years, consistent with most reports in non-Asian populations [18, 32].

Regarding clinicopathological characteristics, our analysis confirms several findings consistent with prior reports, including a higher female proportion and significantly elevated rates of poor prognosis disease-related factors among younger patients (diffuse histology, signet-ring cells, poorly-differentiated tumors, primary metastatic disease, peritoneal dissemination, and ascites) [5–35]. The increased prevalence in young adult females, a near-universal finding in epidemiological GCYA studies, lacks a clear explanation. Some hypotheses suggest hormonal factors, such as high estrogen receptor expression in GEAC cells, may be involved [53–56]. Furthermore, men are more frequently exposed to well-established environmental risk factors like alcohol consumption and smoking, which involve a sequence of preneoplastic lesions that take longer to develop, thus contributing to increased incidence later in life.

The increased aggressiveness in GCYA patients may be attributed to genetic factors, including CDH1 gene alterations that predispose individuals to early-onset diffuse GEAC. Molecular analysis of diffuse-type GEAC has revealed a higher frequency of somatic CDH1 mutations in early-onset cases compared to late-onset ones [57]. These diffuse-type tumors often lack intercellular adhesion, exhibiting aggressive growth patterns and heightened metastatic potential. Additionally, the TCGA analysis indicates that microsatellite instability-high (MSI-H) tumors, typically associated with better prognosis [58], are more common in elderly patients [59], potentially contributing to the more aggressive tumor biology in GCYA. Finally, GCYA often experiences delayed diagnosis, resulting in advanced disease at presentation. Many GCYA cases lack alarm symptoms, leading to GEAC not being considered in the differential diagnosis for young individuals with gastrointestinal symptomatology [60]. Consequently, they are less likely to undergo endoscopic screening, particularly in low-incidence areas, leading to a diagnosis delay. In our series, a higher percentage of young patients had primary metastatic tumors compared to older patients (87.1% vs. 79.5%; $p = 0.003$) (Table 1), and this feature was associated with poorer survival (Table 4).

Very limited data is available to date regarding potential age-related differences in treatment outcomes and toxicity with standard CT. Existing real-world data essentially come from small, retrospective studies, most of which have included heterogeneous GEAC cohorts with any tumor stage [3, 7, 9–13, 18, 23, 25]. In contrast, our study specifically focused on advanced GEAC patients eligible for first-line combination CT and included a larger, well-defined cohort of both younger and older individuals. Notably, only two Japanese reports have focused on systemic CT for the treatment of advanced GCYA thus far [10, 11]. However, both included fairly small populations -87 and 20 patients in Nakayama [10] and Yamamoto [11] cohorts, respectively-, heterogeneously treated with both platinum-doublet CT or monotherapy for any line of advanced disease, thus making comparisons with our results somewhat challenging.

In our study, despite the increased use of triple-agent CT in younger patients compared to older ones, we did not observe significant differences in survival between doublet and triplet regimens. Based on these results, which are aligned with data from prior studies [61–63], and the higher levels of toxicity over doublet regimens, we cannot recommend first-line triplet CT as a standard approach either in the whole series or in the younger cohort [38]. In contrast, primary tumor and metastases showed to improve outcomes in our population, in accordance with the protective role of metastases resections suggested by preceding analyses from the AGAMENON-SEOM registry [64]. While the current evidence from prospective trials regarding the potential survival benefit of primary tumor or metastases surgery remains inconclusive [43, 44], our data may support the consideration of surgery as an individualized approach for highly selected younger patients with oligometastatic disease and response to CT.

Efficacy outcomes were similar in our analysis for both younger and older populations, even after adjusting for potential confounding factors. Although conflicting findings regarding GCYA survival have been published over years, most recent analyses indicate that young adults perform as well as [3, 7, 16, 19, 21, 23, 24, 26–32, 35–37] or even better [9, 33, 34] than older patients, particularly when stage-specific survival was examined. Asian studies focused on advanced GEAC disease have also reported inconsistent results. Whereas Nakayama found standard CT may have similar efficacy in GCYA compared to the general-aged population included in pivotal clinical trials [10], Yamamoto reported worse OS in young patients than in the middle-aged group [11].

Table 5 Adverse events based on age (< 45 and ≥ 45 years) and CT schedule

	Oxaliplatin + FP regimen				Cisplatin + FP regimen				Anthracycline triplet				Docetaxel triplet				Others			
	< 45 years		≥ 45 years		< 45 years		≥ 45 years		< 45 years		≥ 45 years		< 45 years		≥ 45 years		< 45 years		≥ 45 years	
	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)	Any (%)	≥ G3 (%)
Anemia	65.6	8.6	64.4	6.1	**78**	6	**63**	6.3	60.3	**1.4**	62.2	**7.6**	69	6.9	69.7	12.7	73.3	6.7	63.2	6.9
Neutropenia	41.9	17.2	41.2	16.9	56	22	51.7	20.7	56	31.5	50.1	26.3	34.5	13.8	50	22.5	**63.3**	**33.3**	**41.4**	**17.8**
Febrile neutropenia	5.4	–	4.3	–	2	–	5.3	–	4.1	–	7.6	–	6.9	–	8.5	–	**16.7**	–	**4.9**	–
Thrombocytopenia	24.7	2.2	28.5	2.7	12	4	17.1	1.9	19.2	5.5	21.7	2.6	6.9	0	22.5	1.4	26.7	3.3	16.1	2.3
Nausea	65.6	4.3	57	3.1	62	2	59.8	4.3	**65.8**	2.7	**52.4**	4.2	44.8	3.4	66.4	2.8	66.7	0	49.4	2.9
Vomiting	43	3.2	35.3	3.1	46	4	35.6	3.1	**49.3**	6.8	**31.9**	4.5	31	3.4	38.7	3.5	46.7	3.3	29.9	3.2
Diarrhea	38.7	4.3	43.3	6.5	42	4	35.8	4.1	35.6	5.5	35.2	4.9	41.4	6.9	45.8	5.6	43.3	6.7	35.3	5.7
Stomatitis	25.8	0	31.7	2.9	34	4	32.9	3.4	30.1	2.7	31	3.8	**20.7**	3.4	**42.3**	4.9	33.3	0	29.9	0.9
Fatigue	67.7	4.3	70.5	8.4	80	4	68	6.2	56.2	2.7	56.3	5.1	69	10.3	73.2	9.9	73.3	3.3	67.2	6.9
HFS	19.4	2.2	24.5	2.4	32	2	33.6	1.5	20.5	2.7	24.6	2.5	30.5	13.8	44.4	10.6	3.3	3.3	14.7	0.9
Neuropathy	59.1	4.3	66.6	5.2	24	0	25.3	1.2	49.3	2.7	52.2	3.4	48.3	**13.8**	55.6	**3.5**	30	3.3	22.4	2.3
Alopecia	**15.1**	2.2	**8.9**	2.5	18	0	18.3	2.4	46.4	**1.4**	44.6	**8.1**	41.4	3.3	60.6	2.9	**56.7**	3.3	**29.3**	2.9
Hyperbilirubinemia	11.8	2.2	8.3	1.8	**10**	**0**	**3.3**	0.7	9.6	4.1	5.9	0.9	6.9	3.4	5.6	1.4	6.7	3.3	3.2	0.6
Increased AST	**30.1**	**4.3**	**15.1**	**1**	8	**4**	7.5	**0.5**	13.7	1.4	14	0.8	27.6	3.4	13.4	1.4	6.7	3.3	9.8	1.4
VTE	7.5	3.2	7.6	3.9	28	**18**	12	**5.7**	15	8.2	10	5.3	6.9	3.4	2.8	0	6.7	3.3	8.3	4
Renal toxicity	**1.1**	0	**6.6**	0.3	6	2	9.1	1.5	8.2	1.4	7.6	0.4	13.4	3.4	4.9	0.7	3.3	1.1	7.8	0.6
Cardiotoxicity	0	0	1.8	0.8	4	2	2.9	1	0	0	2.6	0	0	0	0	0	0.3	0	1.7	0.3
Toxicity-related hospital admission	19		21		22.4		22.7		28.6		25.4		16.7		21.4		16.7		20.9	

Statistically significant differences based on age are marked in bold. AST, aspartate aminotransferase; FP = fluoropyrimidine; HFS, hand-foot syndrome; VTE, venous thromboembolism

Reasons to explain preserved efficacy outcomes in GCYA in our study despite more aggressive tumor biology and advanced disease might include significantly better ECOG-PS and organ function, as well as fewer chronic comorbidities in younger adults. These factors often lead to better tolerance and may facilitate the administration of higher doses for specific regimens. Additionally, the greater proportion of younger patients receiving second-line therapies, a well-established positive prognostic factor [65], and/or undergoing surgery for primary tumors or metastases may also contribute to improved survival.

As for the safety profile, despite younger patients received more triplet-based CT and higher dose intensity for specific regimens, they did not consistently experience more toxicity than older individuals, and fewer patients had to discontinue treatment due to adverse effects. The higher incidence of emesis in younger patients, particularly in those treated with anthracycline-based triplets, may be attributed to their increased susceptibility, as previously reported in other studies [66]. The elevated rate of grade ≥ 3 VTE in younger patients treated with cisplatin-fluoropyrimidine CT might be attributed to the higher risk of thromboembolic events associated with cisplatin and the greater number of surgeries with subsequent post-surgical immobilization in this age group. These findings, although not entirely consistent with those reported in other series of advanced GCYA [10], also suggest that worse functional status and the presence of significant comorbidities, both more frequent in older patients, may have a greater impact on the risk of toxicities than the intensity of the CT itself.

Among the limitations of this study are the healthcare nature of the sample, with the repercussions that this can have on the accuracy of epidemiological variables, treatment response and toxicities. Nevertheless, most prior reports have also been based on real world registries and this may be even an asset when assessing treatment patterns that may differ based on age in clinical practice. Secondly, the composition of first-line polychemotherapy has evolved over time, which may have played a role in the selection of different CT regimens in a study involving patients over a 14-year period. Conversely, the inclusion of patients deemed fit enough to be treated with standard, front-line combination CT excluded other less intensive treatments (monotherapy) and best supportive care alone, thus precluding the analysis of a potential differential first-line therapeutic approach for a given age or patient and/or disease profile. Furthermore, most patients were treated before the widespread adoption of immunotherapy in combination with CT as the first-line standard of care, so further analysis will be needed soon to assess potential differences in efficacy-related outcomes and toxicity according to age. Thirdly, given the retrospective nature of the analysis, some well-established risk factors, including Helicobacter pylori infection, family cancer history or inherited cancer predisposition syndromes, and prevalent genetic aberrations in GCYA like mutations in CDH1, Ras homolog gene family A (RhoA) or CLDN18-ACRG rearrangements, were not collected. Acquiring more information concerning these variables would be desirable for the purpose of an in-depth analysis to recognize which alterations play the most crucial role in GCYA development and to identify new treatment targets. Finally, despite the large study population and the strong representativeness of Spain, we cannot exclude the possibility that variability in clinical practice with respect to other countries or cultural differences may limit the external validity of our findings. This is further emphasized by the fact that we do not have data on the ethnicity of our patients.

In conclusion, our study shows that, despite GCYA is characterized by the presence of clinicopathological features consistently associated with poor prognosis, combination therapeutic strategies like those used for general-age GEAC cancer patients obtain comparable outcomes in terms of survival-based endpoints and toxicity profile. This may be probably explained for the favorable general condition and fewer comorbidities of younger patients, which allow more extensive treatment approaches, particularly higher rates of surgery for advanced disease and second-line systemic therapies. Based on these data, further prospective studies addressing the potential survival benefit of these therapeutic modalities in younger patients are warranted to better understand our findings.

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Author contributions PPW, AC, JG, ACB and PJF developed the project, analyzed the data, and drafted the manuscript. ILG has analyzed the data. The other authors recruited patients and provided clinical information, comments, and improvements to the manuscript. All authors participated in the interpretation and discussion of data, and the critical review of the manuscript.

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Declarations

Conflicts of interest AC declares she has received payment or honoraria for lectures, presentations, speakers, bureaus, manuscript writing, educational events or participation on a data safety monitoring board

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