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Characteristics of Gastric Cancer in Young Adults: Insights from a Population-Based Study of 46,110 Cases in the German Clinical Cancer Registry Group

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ABSTRACT

Gastric cancer occurring at a younger age, referred to as early-onset gastric cancer (EOGC), represents 2–8% of all cases. This study aimed to define and describe this younger patient population using registry data. Patient records from the German Cancer Registry Group of the Society of German Tumor Centers—Network for Care, Quality and Research in Oncology (ADT) between 2000 and 2016 were examined. Age percentiles were used to stratify histological subtypes of gastric adenocarcinoma, allowing precise identification of EOGC. Demographics, tumor characteristics, therapeutic approaches, and survival outcomes were analyzed.

Out of 46,110 patients, the youngest 20% displayed a higher prevalence of signet ring cell carcinoma (SRCC), surpassing the combined occurrence of diffuse and intestinal subtypes; this group, with a median age of 53, was designated as EOGC. Female representation was slightly lower in EOGC compared to older patients (43% vs. 45%; $p < 0.001$). Younger patients more frequently presented with aggressive disease: poorly differentiated tumors (G3/4: 77% vs. 62%), advanced T stage (T3/4: 51% vs. 48%), nodal involvement (57% vs. 53%), and distant metastasis (35% vs. 30%; $p < 0.001$). Curative treatment was less commonly administered (42% vs. 52%; $p < 0.001$). Despite these adverse features, five-year survival was higher in the EOGC cohort (44% vs. 31%; $p < 0.0001$), with age identified as an independent predictor of better prognosis (HR 0.61; $p < 0.0001$). Using a population-based approach, this study objectively defines the EOGC population and highlights that, although younger patients present with more aggressive tumors and are less frequently treated curatively, their survival is superior to that of older patients, with younger age serving as a strong independent predictor of improved outcome.

Keywords: Gastric cancer in young patients, Early-onset gastric cancer patients, German clinical cancer registry group, EOGC

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Introduction

Gastric cancer (GC) remains a major global health concern, with roughly one million new cases and 769,000 deaths attributed to the disease in 2020, making it the fifth most common cancer and the fourth leading cause of cancer-related mortality worldwide [1]. GC predominantly affects middle-aged and older adults, typically between 50 and 70 years of age, and in Western populations, over half of patients are older than 70 years at diagnosis [2–5]. Nonetheless, 2–8% of cases arise in younger individuals, classified as early-onset gastric cancer (EOGC) [6, 7]. While the incidence of GC in older age groups has declined over recent decades—likely due to H. pylori eradication and improvements in food preservation [1, 8]—EOGC rates have remained stable or even shown slight increases [9].

Research on EOGC is limited, partly because the definition of "early-onset" varies widely across studies [2, 10–12]. Existing literature indicates that EOGC is often associated with more aggressive tumor behavior, including advanced stage at diagnosis, undifferentiated histology, and lymphovascular invasion [13]. However, the prognosis for younger patients is inconsistent, with some studies reporting poorer survival compared to older cohorts [11, 14–16], whereas others have found comparable or even superior outcomes [10, 17, 18].

Given the lack of robust, population-level evidence, this study sought to systematically define and characterize EOGC using data from the German Cancer Registry Group of the Society of German Tumor Centers—Network for Care, Quality and Research in Oncology (ADT).

Materials and Methods

Study population

This retrospective, population-based analysis used data from the ADT, which currently includes 61 member centers. In collaboration with the German Cancer Society (DKG) and the German Cancer Aid (DKH), the ADT collects standardized clinical cancer data nationwide to support research, quality assurance, and improved care. For this study, records of patients diagnosed with gastric cancer (ICD-10: C16) between 2000 and 2016 were extracted. Due to clinically relevant differences between tumors located at the cardia/gastroesophageal junction and those in other stomach regions—such as variations in histology, age and sex distribution, and treatment approaches—tumors of the cardia (ICD 16.0) were excluded, and analyses focused on cancers in the remaining stomach (ICD-10: C16.1–C16.9).

Study parameters

Data underwent quality checks to remove duplicates and exclude patients with missing or implausible information (e.g., missing date of diagnosis or birth, death certificate only, death prior to diagnosis, diagnosis outside 2000–2016, or incorrect ICD-10 codes). Collected variables included demographics (age at diagnosis, sex), tumor characteristics (histology per ICD-O-3, differentiation, pretherapeutic TNM stage, ICD-10 code), treatment modalities (curative: combinations of neoadjuvant therapy, surgery, adjuvant therapy, chemoradiotherapy; palliative: non-curative surgery or chemo/radiotherapy), and follow-up data (90-day postoperative mortality, overall survival).

Identification of early-onset gastric cancer

To define EOGC, the age distribution of the entire cohort and the three major adenocarcinoma subtypes (intestinal, diffuse, signet ring cell carcinoma [SRCC]) was first examined for early peaks in incidence. Subsequently, the relative proportions of these subtypes were assessed across age percentiles. Patients were classified as EOGC if the relative incidence of SRCC exceeded the combined incidence of intestinal and diffuse types. This percentile-based approach avoided arbitrary age cut-offs (e.g., <50 or <60 years).

Statistical analysis and ethics

Analyses were performed using R (version 3.5.1). Categorical variables were reported as counts and percentages, and comparisons used Chi-square tests. Continuous variables were expressed as means with confidence intervals or medians with interquartile ranges. Data visualization included pie and bar charts. Overall survival (OS) was estimated via Kaplan-Meier curves, with group comparisons using the log-rank test. Univariate and multivariate Cox regression identified independent predictors of survival. Significance was defined as $p \leq 0.05$. The study received approval from the Institutional Ethics Committee of the University of Lübeck (Aktenzeichen: 20-237) and the ADT.

Results and Discussion

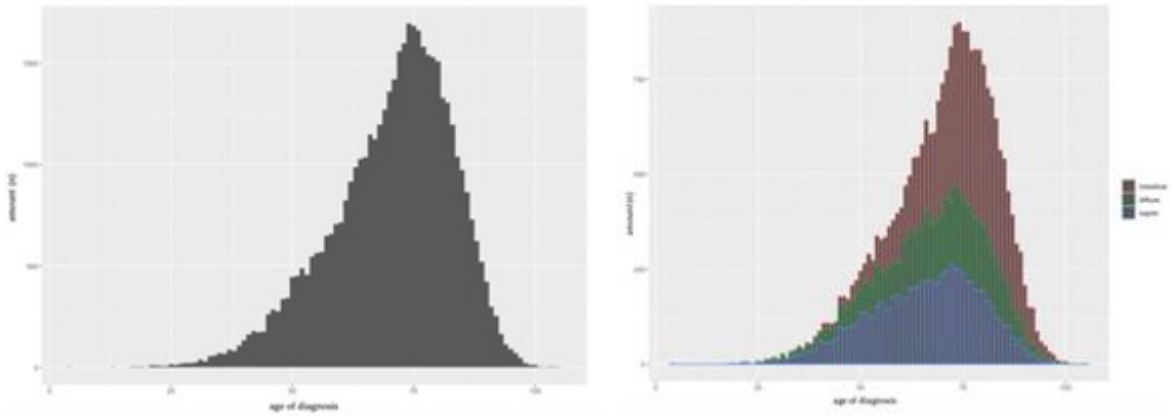
Study population

Between 2000 and 2016, 46,110 patients with gastric cancer (C16.1–C16.9) were recorded in the ADT registry, representing approximately 20% of all cases in Germany during this period, according to the Association of Population-Based Cancer Registries in Germany (GEKID). The overall cohort included 45% female and 55% male patients (male-to-female ratio 1.22:1), with a median age at diagnosis of 72 years. Women were slightly older than men (median 74 vs. 71 years).

Definition of early-onset gastric cancer patients

Age distribution for the entire cohort and the three adenocarcinoma subtypes is shown in **Figure 1**. Overall, the population showed a peak incidence at 74 years (median 72 years; IQR 63–80). Each histological subtype mirrored this peak. No distinct secondary peak was observed at younger ages. However, median age varied by subtype:

SRCC patients were youngest (median 67.2 years; IQR 56–76), followed by diffuse type (70 years; IQR 60–78), and intestinal type (75 years; IQR 68–82).



a) b)

Figure 1. Gastric Cancer Cohort. Left panel: age distribution of the overall population. Right panel: age distribution by histological subtype; red indicates intestinal type, green represents diffuse type, and blue denotes signet ring cell carcinoma (SRCC).

Given the observed differences in median age among the three main adenocarcinoma subtypes, we next examined their relative proportions across age percentiles. This analysis revealed a clear trend: as patient age decreased, the prevalence of SRCC increased markedly **(Figure 2)**. Among the youngest 50% of patients, 41% were diagnosed with SRCC. This proportion rose to 49% in the youngest 20%, 53% in the youngest 10%, and reached 57% within the youngest 5% of the cohort.

a) b) c) d)

Figure 2. Relative frequencies of the three main gastric adenocarcinoma subtypes across age percentiles: (a) youngest 50% (<72.4 years), (b) youngest 20% (<60.4 years), (c) youngest 10% (<52.8 years), (d) youngest 5% (<47.1 years).

Examination of age-stratified histology revealed that SRCC became the dominant subtype in patients younger than approximately 60 years, surpassing the combined occurrence of intestinal and diffuse carcinomas. Since this threshold roughly coincided with the division between the youngest 20% and the older 80% of patients, we defined the youngest 20% as early-onset gastric cancer (EOGC) and the remaining 80% as late-onset gastric cancer (LOGC).

Profile of early-onset gastric cancer patients

Within the cohort, 9,221 individuals met the criteria for EOGC, while 36,889 were classified as LOGC. The median age of the EOGC group was 53 years, more than two decades younger than the LOGC median of 75 years. Female patients comprised a slightly smaller fraction of the EOGC cohort compared with LOGC (43% vs. 45%; $p < 0.001$). Adenocarcinoma was the predominant tumor type in both groups, yet it was somewhat less frequent among EOGC patients (87% vs. 90%; $p < 0.001$). In contrast, gastrointestinal stromal tumors (GIST) and neuroendocrine tumors were more frequently observed in younger patients (3.4% vs. 2.6% for GIST; 3.9% vs. 2.1% for neuroendocrine tumors; $p < 0.001$).

As summarized in **Table 1**, EOGC patients tended to present with more aggressive disease: a higher proportion had poorly differentiated tumors (G3/4: 77% vs. 62%), more advanced T stage (T3/4: 51% vs. 48%), increased nodal involvement (57% vs. 53%), and more frequent metastases (35% vs. 30%) compared with the LOGC population.

Table 1. Overview of tumor characteristics (TNM-/G-stage) in both groups.

TNM-Status	Stages	EOGC	LOGC	p-Value
Grading (n = 7573 versus 31,342)	G1	458	2162	p < 0.001
Proline+nanosilver		6.0%	6.9%	
	G2	1292	9813	
		17.1%	31.3%	
	G3	5557	18,529	
		73.4%	59.1%	
	G4	266	838	
		3.5%	2.7%	
T stage (n = 5105 versus 18,835)	T1	1094	4344	
Tyrosine+nanosilver		21.4%	23.1%	
	T2	1425	5514	p < 0.001
		27.9%	29.3%	
	T3	1638	5817	
		32.1%	30.9%	
	T4	948	3160	
		18.6%	16.8%	
N stage (n = 5029 versus 18,641)	N0	2154	8860	p < 0.001
Histidine+nanosilver		42.8%	47.5%	
	N+	2875	9781	
		57.2%	52.5%	
M stage (n = 5140 versus 18,096)	M0	3356	12,751	p < 0.001
Arginine+nanosilver		65.3%	70.5%	
	M+	1784	5345	
		34.7%	29.5%	

Figure 3 illustrates the distribution of treatment strategies among EOGC and LOGC patients. Overall, younger patients were less likely to undergo curative-intent therapy compared with older patients (42% vs. 52%), including curative surgery with or without additional therapy (36% vs. 49%; $p < 0.001$). Examining individual curative approaches in more detail, the proportion of EOGC patients receiving surgery alone without any documented adjunctive therapy was roughly half that observed in the LOGC group. Conversely, other curative modalities—particularly multimodal strategies such as neoadjuvant or adjuvant therapy combined with surgery, as well as definitive chemoradiotherapy—were applied more frequently in the EOGC cohort.

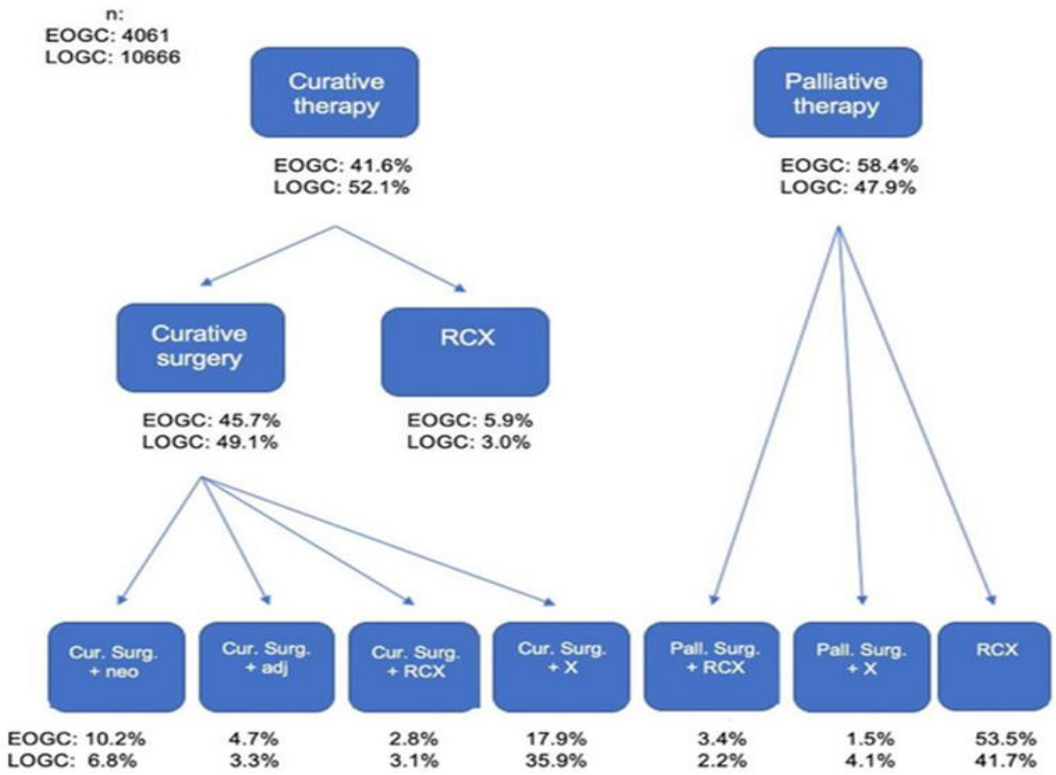


Figure 3. Treatment algorithms in both groups EOGC and LOGC.

The overall median survival for the full cohort was 21.9 months (95% CI: 21.3–22.3), with a five-year survival rate of 33.5% (95% CI: 32.9–34.1). Notably, patients in the EOGC group had substantially longer median survival at 38.6 months (95% CI: 34.6–42), compared with 19.2 months (95% CI: 18.3–19.7) in the LOGC group ($p < 0.0001$). Consistent with this, five-year survival was markedly higher among EOGC patients, reaching 44.0% (95% CI: 42.7–45.3) versus 30.6% (95% CI: 30.0–31.3) in LOGC ($p < 0.0001$, **(Figure 4)**).

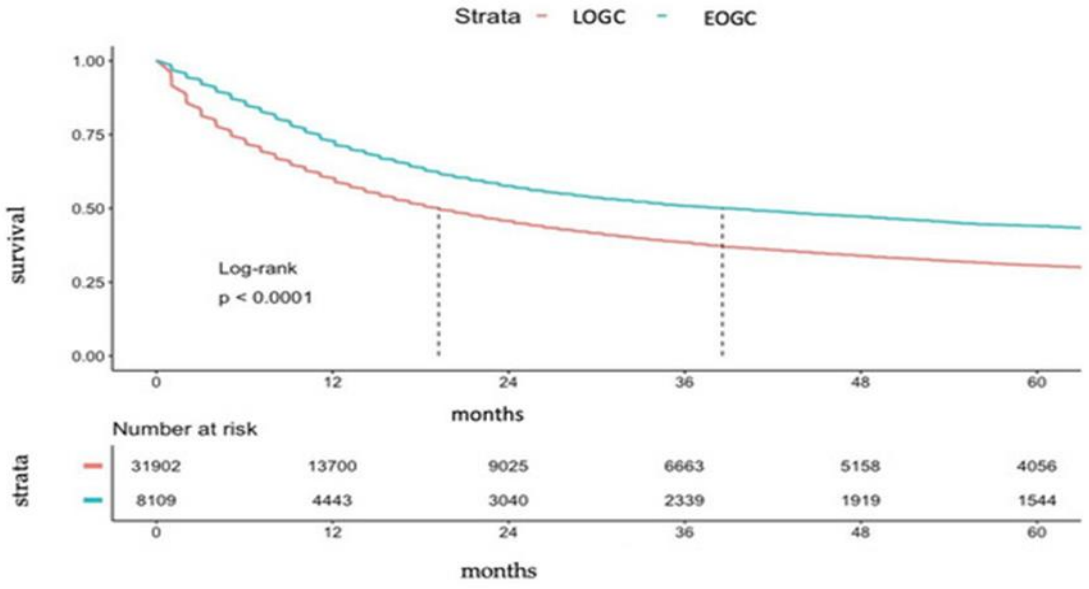


Figure 4. Kaplan-Meier-Curve for survival for EOGC and LOGC.

After excluding early 90-day mortality, the median overall survival for patients undergoing curative surgery with or without additional treatment was 76.4 months (95% CI: 70.6–82.6), with a 5-year survival rate of 56.0% (95% CI: 54.2–57.7), whereas those receiving palliative treatment had a median survival of 15.0 months (95% CI: 14.2–15.3) and a 5-year survival of 16.3% (95% CI: 15.0–17.6). Early-onset gastric cancer (EOGC) patients showed

significantly better survival compared to older-onset patients after both curative and palliative approaches, although the survival advantage was less pronounced in the palliative group **(Table 2)**. Importantly, 90-day mortality was markedly higher in the older-onset gastric cancer (LOGC) cohort (6.7% vs. 1.9%; $p < 0.001$).

Table 2. Median overall survival and five-year survival for curative surgery with/without further treatment and palliative treatment in EOGC and LOGC.

	EOGC		**LOGC**		
	Median Overall survival (months)	5-year survival	Median Overall survival (months)	5-year survival	p-value
Curative surgery with/without further treatment	128.7 (95% CI: 101.5/149.1)	63.6% (95% CI: 60.0/66.9)	68.2% (95% CI: 63.5/73.2)	53.5% (95% CI: 51.5/55.5)	$p < 0.001$
Palliative treatment	16.3 (95% CI: 15.2/17.3)	19.5% (95% CI: 17.2/21.9)	14.2 (95% CI: 13.2/14.9)	14.6% (95% CI: 13.1/16.2)	$p < 0.001$

Univariate Cox regression analyses of the entire cohort identified age, histological tumor type, adenocarcinoma subtypes (SRCC vs. diffuse vs. intestinal), differentiation, and TNM stage as significant factors influencing overall survival [19]. Multivariate Cox regression results for patients with adenocarcinoma are presented in **Table 3**, demonstrating that age, adenocarcinoma subtypes, differentiation, and TNM stage remained independent predictors of survival, whereas sex did not. Notably, in patients undergoing curative-intent surgery with or without additional treatment, histological subtype and differentiation were not independent survival predictors, and in palliative settings, histological subtype and node-positive status did not independently influence survival. However, younger age (EOGC) consistently emerged as an independent predictor of improved survival in both curative and palliative contexts.

Table 3. Multivariate Cox regression analyses on the entire patient population, including only patients with adenocarcinoma histology.

	Multivariat Regression Analysis n = 8976			**Late Onset n = 6779**			**Early Onset n = 2197**		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
female	1			1			1		
male	1.02	0.96–1.09	0.444	1.01	0.95–1.08	0.755	1.09	0.96–1.24	0.174
LOGC/>60.4 years	1								
EOGC/<60.4 years	0.61	0.56–0.65	0.000						
Histological subtype									
intestinal type	1			1			1		
diffuse type	1.13	1.04–1.23	0.003	1.13	1.04–1.24	0.007	1.15	0.94–1.42	0.182
SRC type	1.10	1.02–1.20	0.018	1.09	1.00–1.20	0.058	1.15	0.95–1.41	0.169
Grading									
G1	1.03	0.84–1.27	0.778	1.03	0.83–1.28	0.785	0.80	0.39–1.63	0.530
G2	0.94	0.86–1.02	0.157	0.96	0.87–1.05	0.352	0.80	0.63–1.01	0.060

G3	1			1			1		
G4	1.33	1.15–1.55	0.000	1.27	1.06–1.52	0.009	1.44	1.10–1.88	0.007
T-status									
T1	0.49	0.44–0.55	0.000	0.55	0.49–0.62	0.000	0.31	0.24–0.41	0.000
T2	0.70	0.65–0.76	0.000	0.73	0.67–0.79	0.000	0.61	0.52–0.71	0.000
T3	1			1			1		
T4	1.28	1.18–1.39	0.000	1.30	1.18–1.43	0.000	1.19	1.00–1.41	0.049
N-status									
N0	1			1			1		
N+	1.53	1.42–1.65	0.000	1.58	1.45–1.71	0.000	1.38	1.17–1.62	0.000
M-status									
M0	1			1			1		
M1	2.38	2.23–2.57	0.000	2.24	2.06–2.43	0.000	2.84	2.45–3.28	0.000
	Multivariat regression analysis n = 8976			Curative-operative treatment (>90 days survival) n = 1467			Palliative treatment n = 1434		
	Hazard ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
demographics									
female	1			1			1		
male	1.02	0.96–1.09	0.444	1.02	0.87–1.20	0.792	1.03	0.91–1.18	0.638
o80/>60.4 years	1			1			1		
y20/<60.4 years	0.61	0.56–0.65	0.000	0.58	0.47–0.70	0.000	0.80	0.70–0.93	0.003
Histological subtype									
Intestinal type	1			1			1		
Diffuse type	1.13	1.04–1.23	0.003	1.11	0.89–1.40	0.347	1.15	0.96–1.38	0.117
SRC type	1.10	1.02–1.20	0.018	1.20	0.96–1.51	0.117	1.01	0.84–1.22	0.885
Grading									
G1	1.03	0.84–1.27	0.778	0.99	0.59–1.66	0.970	0.94	0.57–1.55	0.815
G2	0.94	0.86–1.02	0.157	0.84	0.66–1.06	0.136	0.84	0.69–1.03	0.088
G3	1			1			1		
G4	1.33	1.15–1.55	0.000	1.16	0.57–2.34	0.678	1.63	1.14–2.33	0.007
T-status									
T1	0.49	0.44–0.55	0.000	0.42	0.32–0.55	0.000	0.88	0.67–1.16	0.378
T2	0.70	0.65–0.76	0.000	0.69	0.57–0.83	0.000	0.81	0.68–0.96	0.015

T3	1			1			1		
T4	1.28	1.18–1.39	0.000	1.33	1.01–1.76	0.041	1.14	0.98–1.33	0.093
N-status									
N0	1			1			1		
N+	1.53	1.42–1.65	0.000	1.74	1.45–2.08	0.000	0.95	0.81–1.12	0.548
M-status									
M0	1			1			1		
M1	2.38	2.23–2.57	0.000	2.17	1.63–2.89	0.000	2.01	1.75–2.30	0.000

In Western countries, gastric cancer is predominantly diagnosed in older adults [2–5]. Nevertheless, there exists a clinically recognized group of younger patients who develop gastric cancer, referred to as early-onset gastric cancer (EOGC). This subgroup remains poorly characterized due to the rarity of gastric cancer in younger populations and the varying definitions of EOGC in the literature [11, 14, 15, 20]. In this study, we utilized data from the German Cancer Registry Group of the Society of German Tumor Centers—Network for Care, Quality and Research in Oncology (ADT) to define and describe EOGC in a population-based setting, including 46,110 patients diagnosed with gastric cancer (C16.1–C16.9) from 2006 to 2016, representing roughly one-fifth of all cases in Germany during this period.

Previous studies often define EOGC based on arbitrary age cut-offs or relative percentiles, such as the youngest 5% of patients, leading to significant heterogeneity in classification, with reported age thresholds ranging from <34 to <45 years [11, 14, 15, 20]. To our knowledge, only one study incorporated additional patient characteristics, such as survival, to define EOGC [21]. Since there is no distinct early-age incidence peak apart from the main peak at 74 years, defining EOGC purely by age appears inadequate. We therefore stratified adenocarcinoma histological subtypes by age percentiles, comparing the youngest 5%, 10%, 20%, etc., to the incidence of the three main histological subtypes. This analysis revealed that SRCC incidence increased markedly in younger patients, surpassing the combined incidence of diffuse and intestinal subtypes around 60 years of age. Based on this, we defined EOGC as the youngest 20% of patients, yielding a median age of 53 years, slightly higher than most previously reported cohorts [11, 14, 15, 20].

Characterization of EOGC showed a slightly lower proportion of female patients compared to late-onset gastric cancer (LOGC) (43% vs. 45%). Adenocarcinoma remained the predominant tumor type in both groups, although its incidence differed significantly (87% vs. 90%). Additionally, GIST and neuroendocrine tumors were more common in EOGC. While prior studies reported a higher female prevalence in younger patients [14, 15, 20], these typically included only adenocarcinomas. Our analysis, including all histologies, suggested that the lower proportion of females in EOGC was consistent even when restricting to adenocarcinoma alone (43% vs. 45%). SEER data further support these observations, showing similar female proportions below 45 years (43%) and above 70 years (42%), but lower between 45 and 70 years (32%) [10]. Comparing similar age groups in our dataset yielded consistent findings (<45 years: 52%, 45–70 years: 39%, >70 years: 48%), indicating alignment with previous reports, albeit with slight differences due to EOGC definitions. To our knowledge, this study is the first to assess the distribution of all gastric tumor histologies in EOGC beyond adenocarcinoma. Regarding adenocarcinoma subtypes, our findings confirm previous reports that SRCC is more common in younger patients and that SRCC patients generally present at a lower median age [22–24].

In terms of tumor biology, EOGC patients in our cohort exhibited significantly more advanced and poorly differentiated tumors compared to LOGC, consistent with prior reports on differentiation [10, 25] and TNM stage [11, 15]. Possible explanations for these more aggressive presentations include delayed diagnosis due to the low incidence of gastric cancer in younger individuals [15, 25] and a higher prevalence of biologically aggressive subtypes such as SRCC [11, 20].

Our study also found that curative treatment was less frequently applied in EOGC compared to LOGC. Notably, rates of curative surgery without additional treatment in EOGC were nearly half those observed in LOGC, while multimodal treatments or definitive radio-chemotherapy were used more often in the younger cohort. These findings are plausible given the more advanced disease at diagnosis in EOGC and are partially supported by SEER

data, which show that patients under 45 years received curative surgery less frequently than those aged 45–70 years (56% vs. 58%), although patients over 70 underwent curative surgery even less frequently (50%) [10].

Our study demonstrated that patients with early-onset gastric cancer (EOGC) exhibit significantly better survival than those with late-onset gastric cancer (LOGC), both across the entire population and within curative or palliative treatment subgroups. The survival advantage was more pronounced in patients receiving curative therapy, with a roughly 10% difference in five-year survival compared to about 5% in the palliative group. Multivariate analyses restricted to adenocarcinoma patients identified age, histological subtype, differentiation, and TNM stage as independent predictors of survival, whereas sex was not. Notably, histological subtype and differentiation in curative settings, and histological subtype and node-positive status in palliative settings, did not independently predict survival, whereas younger age (EOGC) consistently remained an independent predictor of improved outcomes. While the prognostic influence of factors such as histology, subtype, differentiation, and TNM stage is well established, the effect of age on prognosis remains debated [10, 11, 15, 20, 25, 26]. Some studies have reported poorer survival in EOGC compared to middle-aged or elderly patients [11, 21], whereas more recent reports show equivalent or superior survival in younger patients [10, 20, 23, 26], particularly large SEER-registry studies confirming better outcomes for patients under 45 years compared to those over 66–70 years [10, 26]. Potential explanations for the survival benefit in EOGC include superior performance status and overall physical fitness, which may enhance tolerance to surgical or multimodal treatment [26].

Despite being a large population-based registry study, several limitations must be acknowledged. Data were collected from multiple regional registries, resulting in potential incompleteness or inaccuracies, particularly concerning treatment details. Disease-free survival data were available but lacked reliability, and thus were excluded despite their clinical relevance. The dataset also lacked critical variables, including comorbidities, H. pylori status, precise surgical details (e.g., extent of lymphadenectomy), postoperative complications, and detailed histological information, preventing adjustment for potential confounders. Furthermore, to objectively identify a young patient cohort beyond arbitrary age cut-offs, we stratified adenocarcinoma subtypes by age percentiles rather than using pre-defined age thresholds (e.g., <50 or <60 years), avoiding “random” selection of age limits but limiting comparability with studies using conventional age definitions.

Conclusion

In this large-scale, population-based registry study of 46,110 gastric cancer patients from the German Cancer Registry Group of the Society of German Tumor Centers (ADT), we identified and defined early-onset gastric cancer using age-stratified distributions of histological subtypes of gastric adenocarcinoma. Patients in this cohort, with a median age of 53 years, presented with more aggressive and advanced tumors and underwent curative treatment less frequently. Nevertheless, EOGC patients showed significantly better survival compared to older patients, both overall and when stratified by treatment modality, with young age emerging as an independent predictor of improved survival. These findings underscore the importance of heightened awareness of gastric cancer in younger patients, suggesting that early endoscopic evaluation for nonspecific symptoms could facilitate earlier diagnosis and potentially earlier tumor stages. Additionally, our results support the consideration of aggressive curative interventions in young patients, as favorable outcomes were observed even in the context of advanced disease.

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Conflict of Interest: None

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Ethics Statement: None

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