Clinical Features and Survival of Young Adults with Stage IV Gastric Cancer: A Japanese Population-based Study

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Abstract

Purpose: With the aging of society, the age of patients with gastric cancer (GC) in Japan has been increasing. However, there are few documented outcomes for young patients with stage IV GC. We investigated the clinical characteristics and prognosis of patients with stage IV GC aged under 40 years using a dataset from an integrated population-based cohort study.

Methods: We conducted this multicenter population-based cohort study to determine whether earlier onset of GC was a poor prognostic factor. We enrolled patients with metastatic GC aged under 40 years (young group) and those aged between 60 and 75 years (middle-aged group). Patients were histologically diagnosed as having gastric adenocarcinoma. We evaluated the overall survival (OS) of both groups and the hazard ratio (HR) for OS based on age. The adjusted HR with 95% confidence interval (CI) was evaluated using the Cox proportional hazards model after adjusting for confounding factors, including sex, histology, number of metastatic lesions, surgical resection, and chemotherapy.

Results: This study enrolled 555 patients. The patients were classified into the young group (n=20) and the middle-aged group (n=535). The median OS values were 5.7 months and 8.8 months in the young and middle-aged groups, respectively (*P*=0.029). The adjusted HR (95% CI) of the young group was 1.88 (1.17–3.04, *P*=0.009).

Conclusions: Age was an independent prognostic factor in patients with stage IV GC. Further studies investigating the genomic characteristics of GC and exploring more effective chemotherapeutic agents are required.

Introduction

The mean age of patients at onset of gastric cancer (GC) ranges from 60 to 70 years [1–3]. This mean age has gradually increased in Japan [4], possibly because of the drastic decline in the prevalence of *Helicobacter pylori* infection among the younger generation. *H. pylori* infection significantly affects GC development [5,6]). However, approximately 2–10% of patients with GC are aged 40 years or under [7].

Previous reports have demonstrated that the prognosis of young patients with resectable stage I–III GC is similar to or better than that of middle-aged or older patients [3,8–10]. Younger patients have fewer comorbidities and a higher tolerance for surgery and adjuvant chemotherapy than older patients [11,12]. Additionally, they can undergo intensive chemotherapy followed by gastrectomy with adequate lymph node dissection, which improves long-term prognosis [13,14]. However, some young patients present with rapidly progressive disease and distant metastasis. These patients are diagnosed with stage IV GC at the initial presentation. Pathological differences have been observed between younger patients with GC and older patients with atrophic gastritis caused by *H. pylori* infection [15]. Previous reports have shown that poorly differentiated adenocarcinoma, diffuse invasive type, and lymphatic or distant metastasis are more common in younger patients than in older patients [2,3,16]. A treatment strategy for stage IV disease in younger patients should be established. However, most previous studies have focused on the

surgical outcomes of young patients with resectable GC. These studies were limited because data were obtained from a single institute, and there are few documented outcomes of young patients with stage IV GC.

We investigated the clinical characteristics and prognosis of young patients with stage IV GC using a dataset from an integrated population-based cohort study. We hypothesized that the survival time of young patients was worse than that of middle-aged patients.

Patients And Methods

Study design and cohort development

This was a population-based study. All nine hospitals designated for cancer treatment in the Fukushima Prefecture participated in this study. First, patients with stage IV GC were enlisted using hospital-based cancer registries. Subsequently, individual patient data, including age, sex, body mass index, performance status, Charlson comorbidity index [17], discovery of symptoms, site, morphological type, histological type, metastatic sites, number of metastatic lesions, operation type, and chemotherapy, were obtained. We merged the datasets from each participating institute after anonymizing the information.

We enrolled patients in this study if they were diagnosed with GC (International Classification of Diseases, Tenth Revision, C16.0–16.9) and had histologically proven adenocarcinoma (differentiated type, undifferentiated type, and mixed type) from a primary lesion between 2008 and 2015. Patients who were lost to follow-up, had multiple primary cancers, or did not undergo biopsy were excluded.

The protocol, registered at the University Hospital Medical Information Network (UMIN000033718), was approved by the institutional review board of all participating hospitals. This board waived the informed consent requirement in accordance with the Japanese government's Ethical Guidelines for Medical and Health Research Involving Human Subjects, which allow an opt-out approach.

Definition of gastric cancer patient groups

Patients aged under 40 years were classified as "young" patients, whereas those aged 60–75 years were classified as "middle-aged" patients. The age when patients were diagnosed with GC was considered in the analysis. The methods of previous studies and the age distribution histogram between 2008 and 2015 were considered. Figure 1 shows the age distribution histogram of 1366 patients diagnosed with stage IV GC in this period.

Outcomes and statistical analyses

The primary outcome was the young group's hazard ratio (HR) for overall survival (OS). After adjusting for sex, histological type, number of metastatic lesions, primary lesion resection, and chemotherapy as confounding factors, we calculated the HR and 95% confidence interval (CI) of both groups using the Cox proportional hazards model. Kaplan-Meier curves were used to illustrate the cumulative incidence of

deaths in the young and middle-aged groups, and a log-rank test was performed to compare the OS of these patient groups. Descriptive statistics were also evaluated. Continuous variables were compared using Student's *t*-test, and categorical variables were compared using Fisher's exact test. All statistical tests were two sided, and *P* values ≤ 0.05 were considered statistically significant. All statistical analyses were performed using R software version 4.0.3 (https://www.R-project.org/; Lucent Technologies, Vienna, Austria).

Results

Enrolled patients

Figure 2 presents the patient enrollment flowchart. A total of 555 patients were enrolled in this study. Twenty patients were included in the young group, and 535 patients were included in the middle-aged group. Table 1 shows patient characteristics, and Table 2 shows treatment details in the two groups. Histological types were more differentiated in the middle-aged group and poorly differentiated in the young group ($P = 0.003$). The young group had a lower transition rate to third-line chemotherapy than the middle-aged group ($P = 0.11$).

Table 1
Patient characteristics

Variable		Young (n = 20)	(%)	Middle-aged (n = 535)	(%)
Age (years)	Median (range)	33 (16–39)		68 (60–75)	
Sex	Male	13	65	411	76.8
	Female	7	35	124	23.2
BMI (kg/m^2)	Mean (range)	20.2 (13.0–25.9)		19.7 (10.5–21.3)	
Charlson comorbidity index	0–2	20	100	497	92.9
	> 3	0	0	38	7.1
Discovered based on symptoms	Yes	16	80	251	46.9
	No	4	20	284	53.1
	Detected by cancer screening	0	0	40	7.5
Site	Upper	6	30	134	25
	Middle	13	65	171	32
	Lower	1	5	171	32
	Entire	0	-	54	10.1
Morphological type	Type 4	10	50	94	17.6
	Others	10	50	425	79.4
Histological type	Tub, pap	0	-	186	34.8
	Por, sig, muc	17	85	296	55.3
	Mix	3	15	53	9.9
Metastatic site[a]	Peritoneal dissemination	15	75	279	52.1
	Liver	4	20	206	38.5
	Lymph node	7	35	245	45.8

[a]Some patients had metastasis at more than one site.

BMI, body mass index; tub, tubular adenocarcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; mix, mixed type.

Variable		Young (n = 20)	(%)	Middle-aged (n = 535)	(%)
	Lung	1	5	36	6.7
	Bone	2	10	21	3.9
	Others	3	15	41	7.7
Number of metastatic lesions	One	12	60	302	56.4
	Two	4	20	152	28.4
	Three or more	4	20	69	12.9

[a]Some patients had metastasis at more than one site.

BMI, body mass index; tub, tubular adenocarcinoma; pap, papillary adenocarcinoma; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; mix, mixed type.

Table 2
Treatment details

Variable		Young (n = 20)	(%)	Middle-aged (n = 535)	(%)
Operation	TG	5	25	111	20.7
	DG	2	10	66	12.3
Resection margins	R0	1	5	27	5
	R1, 2	5	25	137	25.6
Chemotherapy	First-line monotherapy	3	15	105	19.6
	First-line combination therapy	14	70	310	57.9
	First-line	17	85	415	77.6
	Second-line	9	45	216	40.4
	Third-line	1	5.0	112	20.9

TG, total gastrectomy; DG, distal gastrectomy.

Adjusted hazard ratios and overall survival curves

Table 3 shows the adjusted HRs for all patients. With the HR of the middle-aged group as a reference, the HR (95% CI) of the young group was 1.88 (1.17–3.04, $P = 0.009$). Figure 3 shows the OS and at-risk

population for both groups. The median OS values were 5.7 months and 8.8 months in the young and middle-aged groups, respectively ($P = 0.029$).

Table 3
Hazard ratios of potential prognostic factors

Variable	Reference	Hazard ratio	95% CI	*P* value
Young	Middle-aged	1.88	1.17–3.04	0.009
Female	Male	0.97	0.79–1.20	0.79
Por, sig, muc	Tub, pap, mix	1.22	1.00–1.44	0.054
Resection of primary lesion	No	0.34	0.27–0.42	< 0.001
Chemotherapy	No	0.25	0.19–0.31	< 0.001
Two or more metastatic lesions	One lesion	1.18	0.98–1.44	0.087

CI, confidence interval; por, poorly differentiated adenocarcinoma; sig, signet-ring cell carcinoma; muc, mucinous adenocarcinoma; tub, tubular adenocarcinoma; pap, papillary adenocarcinoma; mix, mixed type.

Discussion

This study yielded four important results. First, age under 40 years was identified as an independent risk factor for survival. Second, the predominant histological type in the young group was poorly differentiated, and the typical metastatic pattern was peritoneal dissemination. Third, the proportion of patients who received third-line chemotherapy was lower in the young group than in the middle-aged group. Finally, we suggest that the survival of younger patients is worse than that of middle-aged patients.

Previous studies have reported that the prognosis of patients aged under 40 years with stage I–III GC is comparable to or better than that of patients aged ≥ 40 years [4,8–10,18]. We focused on patients with stage IV GC in this study and found that the young group had a worse prognosis than the middle-aged group. Young patients were more likely to have undifferentiated type GC, resulting in a higher incidence of peritoneal dissemination than hematogenous metastasis. Peritoneal dissemination can present with a more rapid progression than liver or lymph node metastasis, and the switch to chemotherapy is often unsuccessful. In the present study, the rate of third-line treatment in young patients was lower than that in middle-aged patients, reflecting the difficulty of treating peritoneal dissemination.

The prevalence of *H. pylori* infection among young Japanese people is low. Therefore, GC development in people aged under 40 years may involve carcinogenesis pathways and biological properties that are different from those of common GC secondary to atrophic gastritis. The molecular mechanisms of gastric carcinogenesis have recently been elucidated, and potential therapeutic targets have been identified based on the classification of molecular subtypes [19]. The genomically stable GC subtype is

more common in younger patients, has the highest resistance to fluorouracil, and is associated with poor prognosis [20]. In addition, the chromosomal instability GC subtype, which is associated with extensive gastric mucosal atrophy owing to *H. pylori* infection, is more sensitive to chemotherapy and has less recurrence after adjuvant therapy than other subtypes [20]. These molecular differences may be related to differences in chemotherapy efficacy and GC progression. Young patients with stage IV GC who already have distant metastasis at the time of diagnosis require shorter intervals between examinations and earlier evaluation of treatment effects.

Previous studies have shown that younger age was not a poor prognostic factor for stage I–III GC [18,21]. However, for stage IV GC, younger age indicated poorer prognosis in our study. Early-onset disease includes rare cases of rapid progression. Patient survival is short when the disease is detected at stage IV.

This study has a few limitations. First, information on *H. pylori* infection and genetic information (*CDH1* mutation, RhoA, microsatellite instability, and loss of heterozygosity) were not collected. Second, the number of cases in the young group was small, which could interfere with the reliability of our results. However, young patients with GC are rare, and stage IV GC cases are uncommon [9,16]. In our study, young patients with stage IV GC accounted for approximately 1.5% of the entire cohort. Therefore, the results of this study are meaningful and distinct since they focused on early-onset stage IV GC.

In conclusion, younger age (under 40 years) was an independent prognostic factor for patients with stage IV GC. Although this is a rather rare population among patients with stage IV GC, further studies investigating the genomic characteristics of GC and exploring more effective chemotherapeutic agents are required.

Declarations

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Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

Availability of data and material

The data that support the findings of this study are available from the corresponding author, M.H., upon reasonable request.

Code availability

The data that support the findings of this study are available from the corresponding author, M.H., upon reasonable request.

Authors' contributions

Category 1

Conception and design of the study: R.Y., M.H., H.K., and H.K.; acquisition of data: M.H., H.K., H.K., and S.H.; and analysis and/or interpretation of data: R.Y. and M.H.

Category 2

Drafting the manuscript: R.Y. and M.H. and revising the manuscript critically for important intellectual content: R.Y. and M.H.

Category 3

Approval of the version of the manuscript to be published: R.Y., M.H., H.K., H.K., K.T., A.M., S.Y., Y.T., S.S., K.K., S.H., T.K., T.I., and N.Y.

Ethics approval

All study procedures were performed in accordance with the ethical standards of the respective committees on human experimentation (institutional and national) and with the Declaration of Helsinki of 1964 and later versions. The study was approved by the institutional review board of all participating institutes.

Consent to participate

The anonymous nature of the data allowed the requirement for informed consent to be waived.

Consent for publication

All authors provided consent for the publication of this study.

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Figures

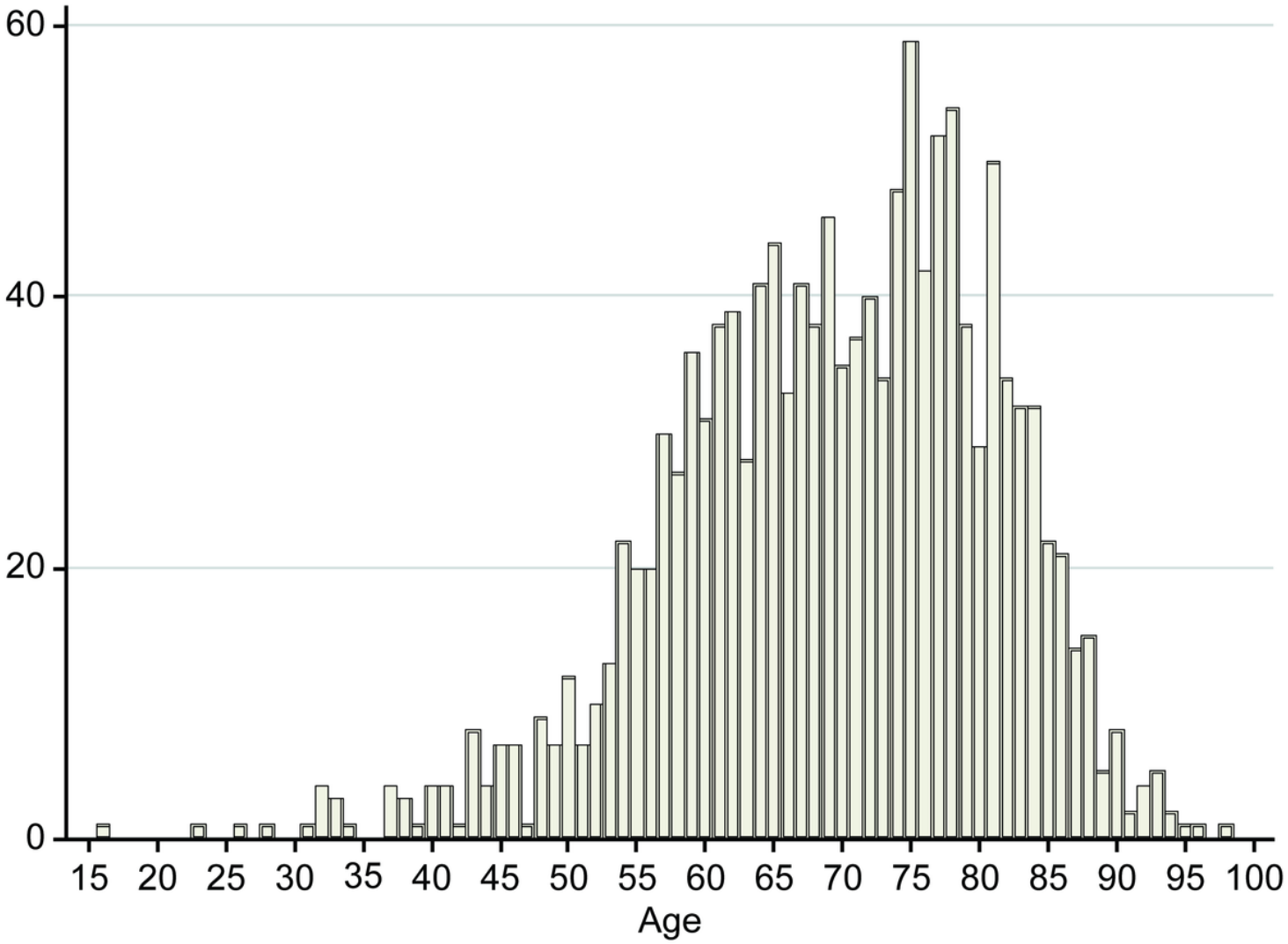


Figure 1

Age distribution histogram for 1366 patients diagnosed with stage IV gastric cancer

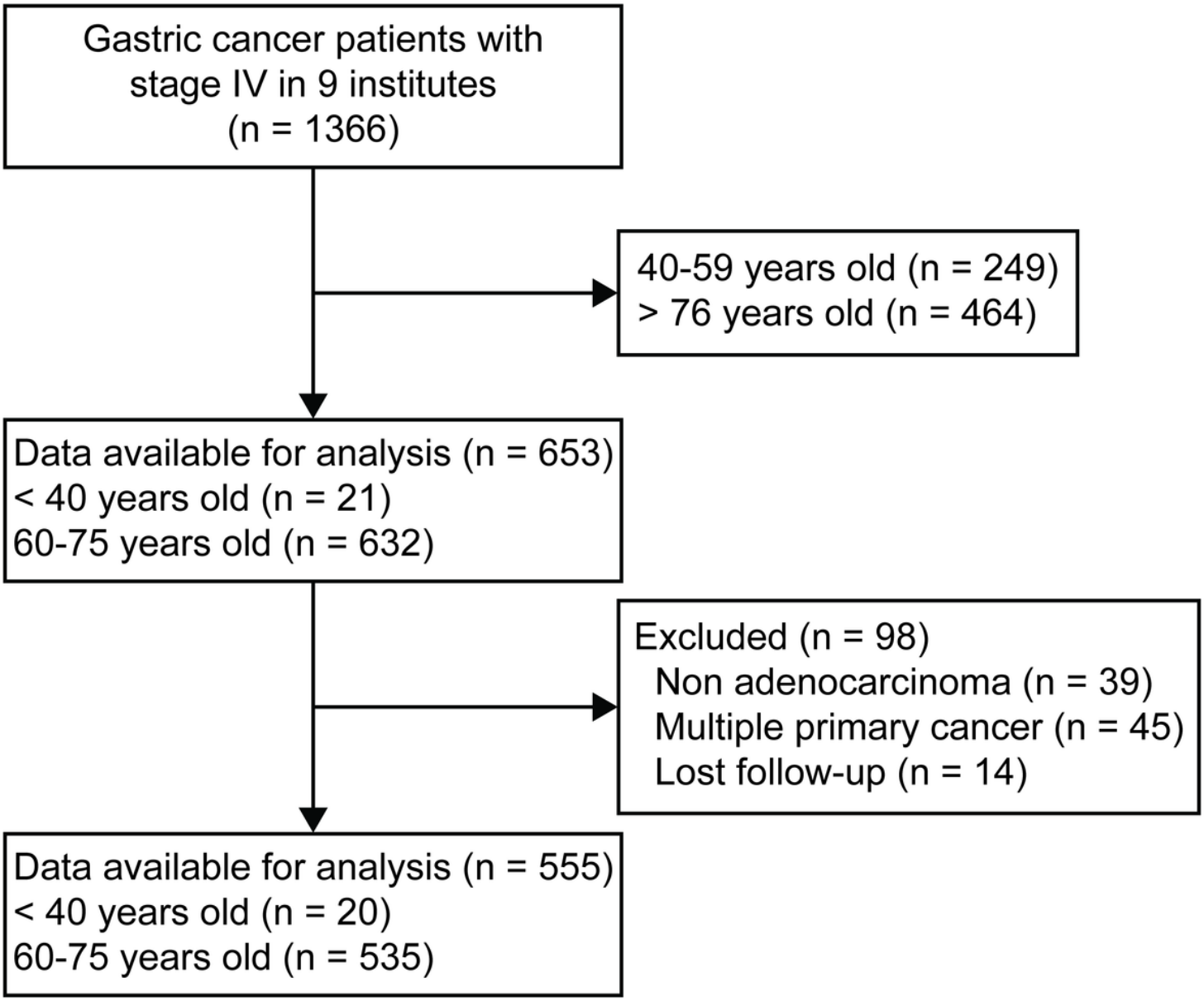
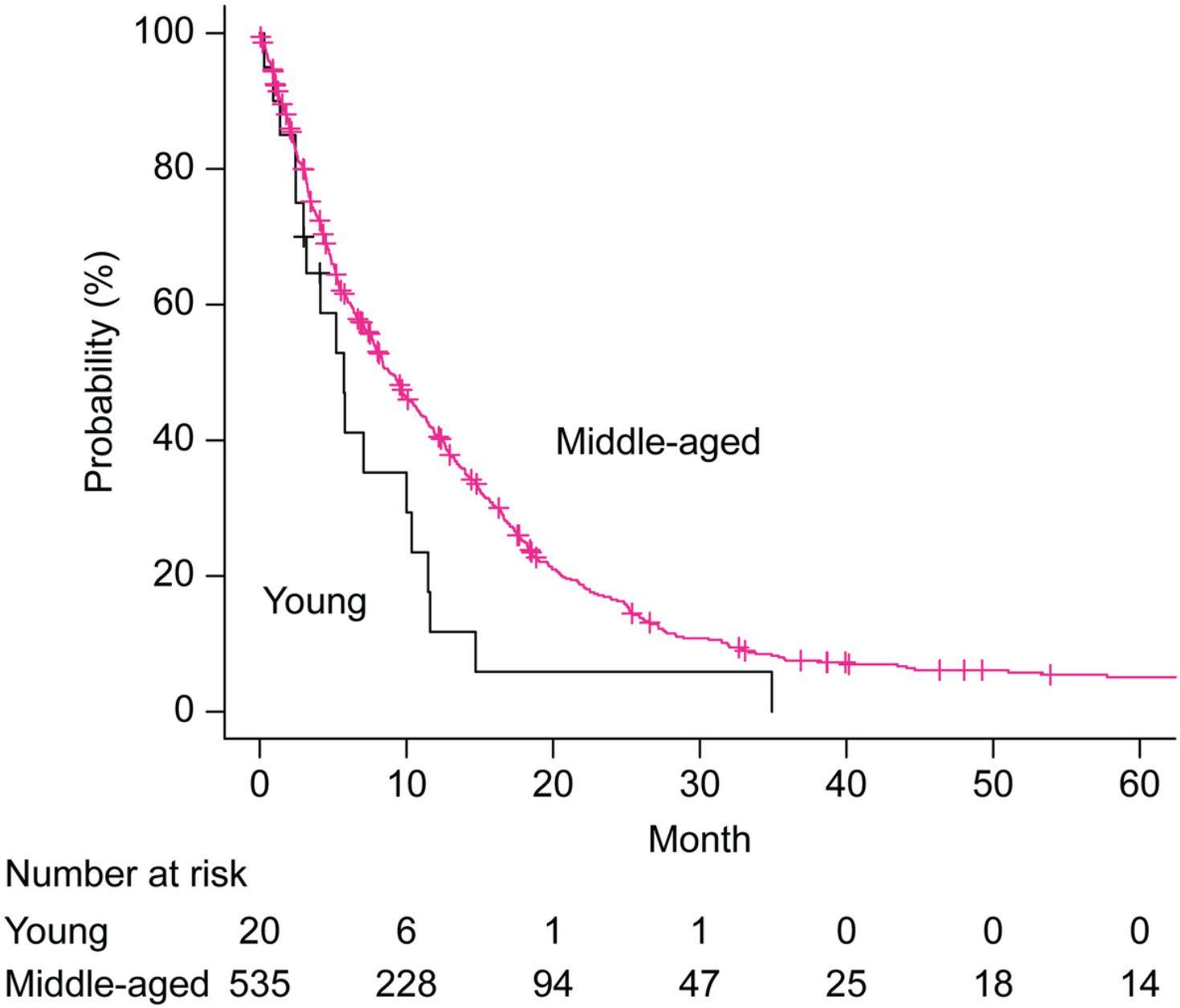


Figure 2

Patient enrollment flowchart. All 555 patients were selected from a population-based cohort of individuals with stage IV gastric cancer



Number at risk

Young	20	6	1	1	0	0	0
Middle-aged	535	228	94	47	25	18	14

Figure 3

Kaplan-Meier curves of overall survival