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ORIGINAL ARTICLE

Clinicopathological Outcomes and Prognosis of Elderly Patients (≥ 65 Years) with Gastric Gastrointestinal Stromal Tumors (GISTs) Undergoing Curative-Intent Resection: a Multicenter Data Review

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Abstract

Background The most common site of gastrointestinal stromal tumors (GISTs) is the stomach, and gastric GISTs (gGISTs) occur most often in elderly patients. However, the clinicopathological features, treatment patterns, and prognosis of elderly patients with gGISTs remain unclear.

Methods We retrospectively *collected clinicopathological and prognostic* data for patients with primary gGISTs who underwent curative-intent resection at 10 medical centers in China from 1998 to 2015.

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Results Over the 18 years, 10 medical centers treated 1846 patients with primary gGISTs by curative-intent resection. The median age was 59 (range 18–91) years. The patients were classified into two groups according to age, namely an elderly group (≥ 65 years of age) and a *nonelderly group* (< 65 years of age). The elderly group had more comorbidities (40.7% vs 23.5%, $p = 0.011$), a higher rate of postoperative complications (14.4% vs 8.7%, $p = 0.031$), and a lower proportion of intermediate/high-risk patients who received adjuvant therapy (30.0% vs 66.8%, $p = 0.001$) than did the nonelderly group. Regarding pathological outcomes, *a significant difference in tumor necrosis* was observed between the two groups ($p = 0.002$), and more cases of tumor necrosis occurred in the elderly group than in the nonelderly group. Regarding postoperative recovery outcomes, *no significant difference was observed between the two groups*. Univariate analysis showed that age, postoperative complications, adjuvant therapy, tumor size, mitotic count, modified National Institutes of Health (NIH) risk category, and tumor necrosis were factors that affected disease-free survival (DFS). Multivariate analysis showed that modified NIH risk category was the only independent factor affecting DFS. The 5-year DFS rates in the nonelderly and elderly groups were 88.1% and 81.4%, respectively ($p = 0.034$), and the 5-year overall survival (OS) rates were 90.4% and 85.5% ($p = 0.038$), respectively.

Conclusions Currently, the treatment patterns for elderly patients with gGISTs remain the same as those for young patients with gGISTs. Elderly gGIST patients had more comorbidities and postoperative complications than did nonelderly gGIST patients, and fewer elderly gGIST patients received postoperative adjuvant therapy. Elderly gGIST patients also had a higher rate of tumor necrosis and worse DFS and OS than did young gGIST patients. Further exploration into the diagnosis and treatment patterns of elderly patients is therefore essential.

Keywords Clinicopathological outcomes · Prognosis · Gastric GIST · Elderly patients

Introduction

Gastrointestinal stromal tumors (GISTs), with a prevalence of 1–2/100,000 individuals, are *potentially malignant tumors that* originate in mesenchymal tissue. These tumors can develop throughout the digestive tract, but the stomach is the most common site, accounting for approximately 60% of all GISTs.[1–3] *Elderly individuals (≥ 65 years)* have a high incidence of cancer, approximately one third of all cancer cases, and GISTs are no exception.[4] The literature suggests that the peak age for the incidence of gastric GISTs (gGISTs) is 58–74 years.[3,5] However, the guidelines for clinical treatment strategies, which are based on the current gGIST literature, were designed for nonelderly patients (< 65 years),[6] and the psychological and physical changes that occur in the elderly can lead to differences between elderly and nonelderly patients in terms of their response to surgery, medications, and prognosis.[4] This study retrospectively analyzed clinical data from 1846 patients with primary gGISTs who underwent curative intent resection from 1998 to 2015 at 10 medical centers in China *to analyze the clinicopathological outcomes and prognosis of elderly (≥ 65 years) gGIST patients*.

Methods

We received *ethics approval for this case* series from 10 medical centers in China (Guangdong General Hospital; Guangdong Academy of Medical Science, Guangzhou, People's Republic of China; Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, People's Republic of China; Southern Medical University Nanfang Hospital, Guangzhou, People's Republic of China; Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou, People's Republic of China; Fujian Medical University Union Hospital, Fuzhou, People's Republic of China; Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China; West China Hospital, Sichuan University, Chengdu, People's Republic of China; Peking University Cancer Hospital and Institute, Beijing, People's Republic of China; Liaoning Cancer Hospital and Institute, Shenyang, People's Republic of China; People's Liberation Army Cancer Center; 81st Hospital of PLA, Nanjing, People's Republic of China). We also received *consent from the patients for the publication of this work*.

Patient Information

Data on *patients with primary gGISTs* who underwent curative intent resection were collected between 1998 and 2015 from the above 10 medical centers in China. The inclusion criteria were as follows: (1) complete clinicopathological data and (2) pathological diagnosis of gGIST. The exclusion criterion was non-tumor-related death.

Observations, Indicators, and Follow-Up

Based on the time of diagnosis, the data were divided into the following six time periods: 1998–2000, 2001–2003, 2004–2006, 2007–2009, 2010–2012, and 2013–2015. Age groups were classified as < 65 years of age (nonelderly group) and ≥ 65 years of age (elderly group). Data on age, sex, comorbidity, tumor location, tumor size, surgical outcome, pathological outcome, adjuvant therapy, *postoperative recovery outcome*, and other clinical and pathological factors were retrospectively analyzed. Survival curves were drawn, and survival between the two groups was compared. According to the modified National Institutes of Health (NIH) risk system,[6] patients were divided by the risk of recurrence and death into very low-, low-, intermediate-, and high-risk groups. The last follow-up visit was recorded on February 15, 2016. Overall survival (OS) was defined as the time from the date of surgery to the last follow-up or death. Tumor-related death indicates that patients died due to gGIST progression or metastasis.

Statistical Analysis

Statistical analyses were performed *using* SPSS software (version 22.0 for Windows; SPSS, Chicago, IL, USA). Categorical data were compared using the chi-squared test or Fisher's exact test. Survival curves were derived from Kaplan-Meier estimates, and the curves were compared using the log-rank test. Variables that were statistically significant ($p < 0.05$) in the univariate analysis were included in a final multivariate Cox proportional hazards model. *All tests were two-sided*, and statistical significance was set at $p < 0.05$.

Results

Patient Information

A total of 1846 patients with primary gGISTs were enrolled in this study (Fig. 1); 918 were male (49.7%) and 928 female (50.3%). Ages ranged from 18 to 91 years (median age was 59). During the 1998–2015 period, the number of patients treated at six 3-year intervals was as follows: 4 cases from 1998 to 2000; 68 cases from 2001 to 2003; 179 cases from 2004 to 2006; 335 cases from 2007 to 2009; 471 cases from 2010 to 2012; and 789 cases from 2013 to 2015 (Fig. 2). All patients were divided into a *nonelderly group* (1264) or an elderly group (582) (Fig. 1).

Comparison Between Groups

No significant differences were observed between the groups in terms of sex, tumor location, gastrectomy range, surgery type, or *multivisceral resection* (Table 1). The incidence of comorbidity (e.g., hypertension, diabetes, coronary heart disease, renal insufficiency, chronic obstructive pulmonary disease) was 23.5% and 40.7% in the nonelderly and elderly groups, respectively (p = 0.011). The incidence of postoperative complications was 14.4% and 8.7% in the nonelderly and elderly groups, respectively (p = 0.031). Of the total number of patients, 462 received postoperative adjuvant therapy (imatinib treatment), and the median adjuvant treatment duration was 21 months (range 3–45 months). Among these patients, 312 (67.5%) were treated with a full course of adjuvant therapy according to the National

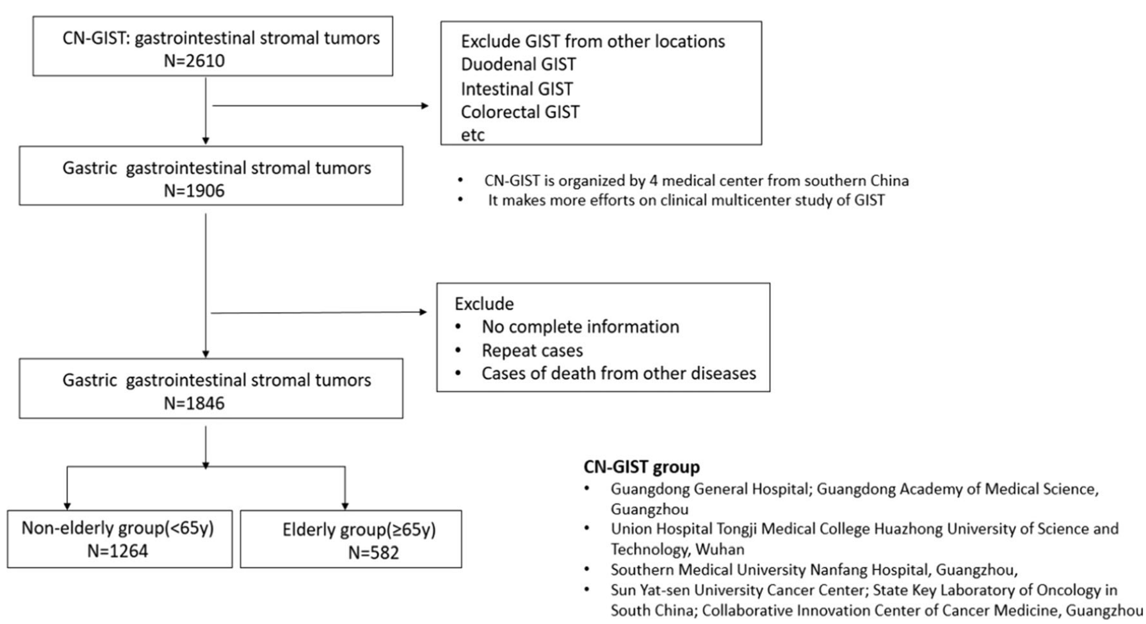

Fig. 1 Study flowchart showing patients with gastric gastrointestinal stromal tumors stratified by age

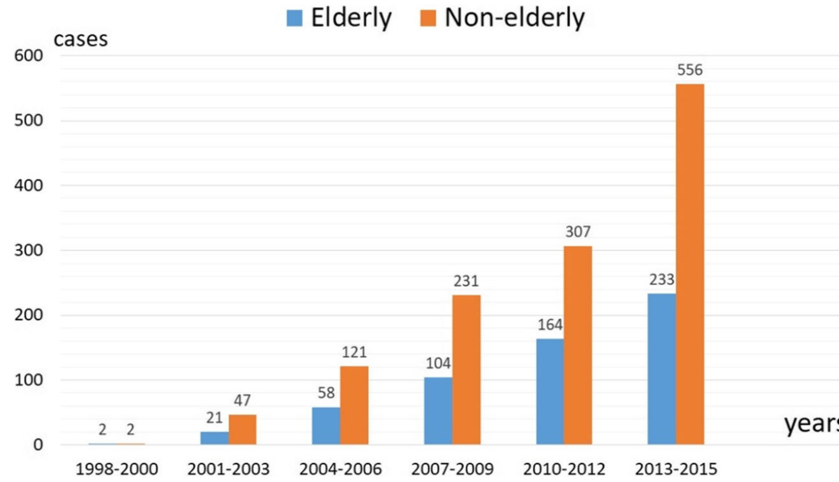

Fig. 2 Patients with primary gGISTs who underwent curative-intent resection in six different time periods

Comprehensive Cancer Network (NCCN) guidelines.[6] In total, 270 cases in the elderly group were intermediate/high risk; only 81 (30.0%) of these patients received adjuvant therapy, with 51 receiving a full course of therapy. Of the 597 intermediate/high-risk patients in the nonelderly group, 381 (66.8%) received adjuvant therapy ($p = 0.001$), and 261 received a full course of therapy. No significant difference in pathological outcome was observed between the two groups in terms of tumor size, mitotic count, tumor rupture, histopathological classification, IHC results, surgical margins, genetic test results, or modified NIH risk category ($p > 0.05$). Of the patients with tumor necrosis, 141 (24.2%) were in the elderly group, and 201 (15.9%) were in the nonelderly group; the difference between these groups was statistically significant ($p = 0.012$) (Table 2). With respect to intraoperative and postoperative recovery outcomes, no significant difference was found between the two groups in terms of operative time, blood loss, time to flatus, diet, time of gastric tube, and drainage tube removal and the length of hospital stay ($p > 0.05$) (Table 3).

Prognosis

The 5-year disease-free survival (DFS) rates in the nonelderly and elderly *groups* were 88.1% and 81.4%, respectively ($p =$ 0.034) (Fig. 3). The median follow-up time for this study was 38 months (range 3–156 months). The 5-year OS rates in the nonelderly and elderly groups were 90.4% and 87.5%, respectively ($p = 0.038$) (Fig. 4).

Univariate and Multivariate Analyses of DFS

Our univariate analysis showed that age, the *occurrence of* postoperative complications, adjuvant therapy, tumor size, mitotic count, tumor necrosis, and modified NIH risk category were all associated with DFS. However, only modified NIH risk category was independently associated with DFS in multivariate analysis: The intermediate-risk (HR 0.057; 95% CI 0.017–0.187; $p = 0.000$) and high-risk (HR 0.279; 95% CI 0.146–0.535; $p = 0.000$) *categories* were independently associated with DFS (Table 4).

Discussion

GISTs are relatively rare mesenchymal tumors with a predilection for the stomach and are characterized by predominant expression of CD34, CD117, and Dog 1.[1,7] According to the modified NIH risk system, tumor site, tumor size, mitotic count, and tumor rupture are indicators of recurrence and prognosis.[6] The highest incidence is found in the 28–74-year-old age group, with the proportion of patients over 65 years of age demonstrating a gradual upward trend.[8,9] Although elderly patients have a predisposition for primary gGISTs, data regarding the diagnosis, treatment, clinicopathological features, and prognosis of elderly individuals with gGISTs are still lacking. An article published in *Annals of Oncology* in 2016[4] reported that elderly patients have become a topic of increasing interest over the past decade and that elderly patients should be analyzed as a subgroup in global, prospective clinical studies, which have gradually been recognized since 2011. That study also showed that 65 years is the primary age threshold used to define elderly patients. In the Z9001[10] and SSGXVIII/AIO[11] trials, in which GIST patients received imatinib adjuvant therapy, subgroup analysis of elderly and nonelderly groups suggested that 65 years should be the landmark by which elderly patients are defined. Therefore, our study defined 65 years as the age threshold for elderly patient status in this analysis.

Elderly individuals may require different treatment modalities and have different prognoses because of deteriorating body functions, decreased immunity, increased comorbidities, and poor compliance. Age may also affect

Table 1 Clinical characteristics and surgical outcomes of patients with gastric GIST stratified by age

Variables	Non-elderly (*N* = 1264)	Elderly (*N* = 582)	*p* value
Gender			0.322
Female	645 (51.0%)	283 (48.6%)	
Male	619 (49.0%)	299 (51.4%)	
Comorbidity			0.011
Presence	297 (23.5%)	237 (40.7%)	
Absence	967 (76.5%)	355 (59.3%)	
Tumor location			0.086
Gastric cardia	69 (5.5%)	38 (6.5%)	
Gastric fundus	508 (40.2%)	227 (39.0%)	
Gastric body	512 (40.5%)	269 (46.2%)	
Gastric antrum	175 (13.8%)	48 (8.3%)	
Range of gastrectomy			0.184
Local resection	992 (78.5%)	442 (75.9%)	
Distal gastrectomy	66 (5.2%)	26 (4.5%)	
Proximal gastrectomy	152 (12.0%)	74 (12.7%)	
Total gastrectomy	54 (4.3%)	40 (6.9%)	
Operative method			0.146
Laparoscopy	651 (51.5%)	273 (46.9%)	
Laparotomy	527 (41.7%)	249 (42.8%)	
Endoscopic surgery	86 (6.8%)	60 (10.3%)	
Multi-visceral resection			0.316
Presence	90 (7.1%)	48 (8.2%)	
Absence	1191 (92.9%)	534 (91.8%)	
Postoperative complications			0.031
Presence	110 (8.7%)	84 (14.4%)	
Absence	1154 (91.3%)	498 (85.6%)	
Adjuvant therapy			0.001
Presence	381 (66.8%)	81 (30.0%)	
Absence	216 (33.2%)	189 (70.0%)	

Comorbidity contains hypertension, diabetes, coronary heart disease, renal insufficiency, chronic obstructive pulmonary disease, etc. Adjuvant therapy is postoperative imatinib treatment. Imatinib is only required for intermediate-risk and high-risk cases defined by modified NIH risk categories. Local resection contains wedge resection, intragastric resection, and endoscopic resection. Endoscopic surgery is defined as the GIST was resected under endoscopy. And, laparoscopic and endoscopic cooperative surgery was enrolled in laparoscopic surgery group

surgical outcomes and be associated with an increased incidence of postoperative complications.[12,13] In this study, the incidence of comorbidities in the elderly group was 40.7% (237/582), which was significantly higher than that in the nonelderly group, at 23.5% (297/1264) (p = 0.011). Farag et al.[5] showed that the complication rate in elderly patients is higher than that in nonelderly patients, and these authors also reported that the increase in comorbidities may affect the ability of elderly gGIST patients to undergo surgery and to complete postoperative adjuvant therapy. In the present study, we found that the elderly group had a significantly higher postoperative complication rate than did the nonelderly group (14.4% vs 9.7%, $p = 0.031$), which may be related to the greater number of comorbidities (40.7%) and open surgery cases (42.8%) in the former. Many studies have reported that the rate of postoperative complications, especially pulmonary complications, in elderly patients is higher than that in young patients. In the elderly, preoperative organ function, specifically cardiovascular and pulmonary functions, should be evaluated; in addition, laparoscopic surgery should be considered to reduce the incidence of postoperative complications.[12–15]

Treatment approaches for elderly patients with gGISTs are currently an area of active exploration.[16,17] In our study, analysis of clinicopathological indicators revealed a significant difference in the use of adjuvant imatinib between the two groups, even though the rate of adjuvant therapy in the elderly group was only 30%, which was lower than the rate of 66.8% in the nonelderly group ($p = 0.001$). In a European multicenter retrospective study,[5] the percentage of elderly patients with gGISTs

Table 2 Pathological outcomes of patients with gastric GIST stratified by age

Variables	Non-elderly (N = 1264)	Elderly (N = 582)	p value
Tumor size			0.212
≤ 2 cm	322 (25.5%)	141 (24.2%)	
> 2-5 cm	506 (40.0%)	216 (37.1%)	
> 5~10 cm	320 (25.3%)	156 (26.8%)	
> 10 cm	116 (9.2%)	69 (11.9%)	
Mitotic count			0.121
≤ 5/50HPF	980 (77.5%)	441 (75.8%)	
> 5~10/50HPF	179 (14.2%)	85 (14.6%)	
> 10/50HPF	105 (8.3%)	56 (9.6%)	
Tumor rupture			0.879
Presence	4 (0.3%)	1 (0.2%)	
Absence	1260 (99.7%)	581 (99.8%)	
Tumor necrosis			0.012
Presence	201 (15.9%)	141 (24.2%)	
Absence	1063 (84.1%)	441 (75.8%)	
Histopathological classification			0.117
Spindle	1194 (94.5%)	546 (93.8%)	
Epitheliod	44 (3.5%)	20 (3.4%)	
Mix	11 (0.9%)	6 (1.0%)	
Non-test	15 (1.2%)	10 (1.7%)	
IHC			0.326
CD34(+)	1084	437	
CD117(+)	1197	541	
Dog-1(+)	1109	512	
No-test	16	15	
Genetic test			0.178
C-KIT 9	7 (0.5%)	2 (0.3%)	
C-KIT 11	138 (10.9%)	65 (11.2%)	
C-KIT 13	1	0	
C-KIT 17	1	0	
PDGFRA 12	3 (0.2%)	1 (0.1%)	
PDGFRA 18	15 (1.2%)	5 (0.9%)	
No-mutation	35 (2.8%)	20 (3.4%)	
No-test	1064 (84.2%)	489 (84.0%)	
Modified NIH risk categories			0.358
Very low-risk	272 (21.4%)	127 (21.8%)	
Low-risk	395 (31.3%)	185 (31.8%)	
Intermediate-risk	299 (23.7%)	125 (21.5%)	
High-risk	298 (23.6%)	145 (24.9%)	

Tumor rupture is defined as tumor rupture causing visual (perioperative or on preoperative imaging scans) spill or described by the pathologist as an entire interruption of the tumor wall and was preexisting before surgery (as described in the surgical report)

HPF high power field, *IHC* immunohistochemistry, *NIH* National Institute of Health

Table 3 Intraoperative and postoperative recovery outcomes of patients with gastric GIST stratified by age

Variables	Non-elderly (N = 1264)	Elderly (N = 582)	p value
Operative time (min)	103.5 ± 68.1	105.7 ± 65.7	0.143
Blood loss (ml)	123.4 ± 312.4	125.7 ± 313.5	0.527
Time to flatus (day)	3.7 ± 1.8	3.8 ± 1.8	0.275
Time to diet (day)	3.6 ± 1.8	3.5 ± 1.6	0.211
Time to remove the gastric tube (day)	3.4 ± 2.1	3.5 ± 2.2	0.432
Time to remove the drainage tube (day)	4.2 ± 1.5	4.3 ± 1.7	0.347
Hospital days (day)	9.2 ± 6.1	9.6 ± 7.3	0.110

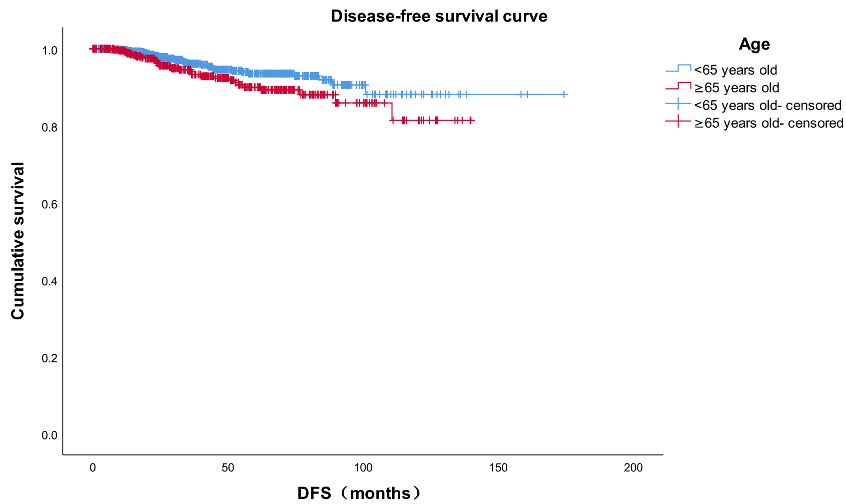

Fig. 3 A disease-free survival curve reveals a significant difference in 5-year DFS rates between the nonelderly group (88.1%) and the elderly group (81.4%) ($p = 0.034$)

who received postoperative adjuvant therapy was 38% compared with 68% among nonelderly patients, a result that was similar to the results of our study. Linda et al.[16] showed age (> 65 years) and risk group to be independent risk factors for postoperative adjuvant therapy in elderly patients with gGISTs. Thus, the current findings suggest that the proportion of elderly patients with GISTs who undergo adjuvant therapy is lower than that of nonelderly patients with GISTs.

Tumor necrosis is a distinct type of cell death that is usually associated with abnormal processes, including exposure to toxins or teratogens, infections, trauma, and ischemia.[18] Studies have shown that tumor necrosis is an independent prognostic factor that affects both DFS and OS in lung, pancreatic, and renal cancers.[19,20] However, no clinical study to date has reported whether the detection rate of tumor necrosis in elderly gGIST patients is different from that in nonelderly gGIST patients. In our study, 24.2% (141/582) cases of tumor necrosis occurred in elderly patients with gGISTs, with 15.9% (201/1264) in nonelderly patients, and the difference between the two groups was statistically significant ($p = 0.012$). These results suggest that the prognosis of elderly patients with GISTs *may be worse than* that of nonelderly patients with GISTs.

Regarding resectable primary gGISTs, studies conducted in the USA,[16] South Korea,[21] and Europe[5] have shown that age is a prognostic factor and that elderly patients with gGISTs have a worse prognosis. In our study, the difference in both the 5-year DFS and OS between the age groups was statistically significant. Univariate analysis showed age to be the influencing factor for DFS. One explanation for this phenomenon may be that the proportion of intermediate/high-risk gGIST patients who underwent postoperative imatinib adjuvant therapy was low. Another explanation may be that elderly gGIST patients had a high rate of tumor necrosis detection. Our multivariate analysis showed that modified NIH risk

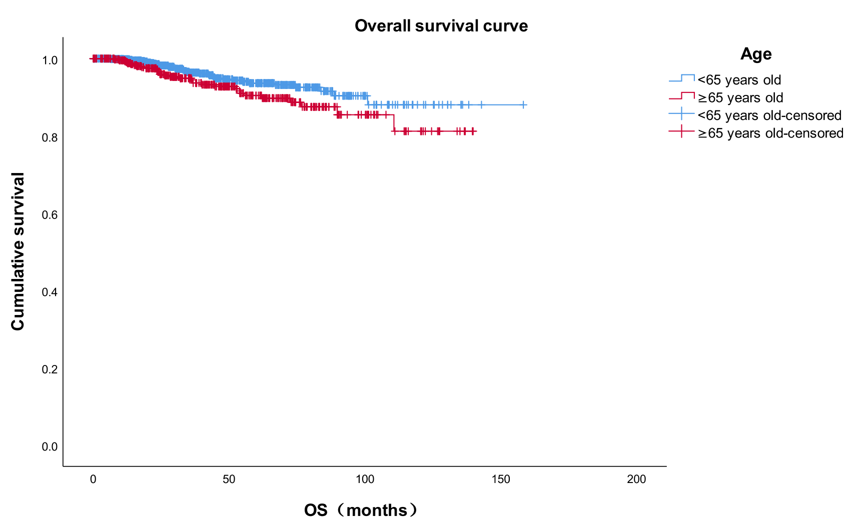

Fig. 4 An overall survival curve reveals a significant difference in 5-year OS rates between the nonelderly group (90.4%) and the elderly group (87.5%) ($p = 0.038$)

Table 4 Univariate and multivariate analyses of disease-free survival in 1846 patients with gastric GIST

	Univariate analysis		Multivariate analysis	
Variables	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender (female)	0.790 (0.493–1.266)	0.327		
Age (< 65 years)	1.638 (1.023–2.623)	0.040	1.186 (0.687–2.050)	0.540
Range of gastrectomy				
Wedge resection	Reference group			
Distal gastrectomy	1.024 (0.658–2.221)	0.902		
Proximal gastrectomy	0.897 (0.337–1.256)	0.914		
Total gastrectomy	0.998 (0.578–1.997)	0.900		
Local resection	1.445 (0.966–2.224)	0.892		
Operative method				
Laparoscopic operation	Reference group			
Laparotomy	1.014 (0.625–2.245)	0.425		
Endoscopic surgery	0.998 (0.237–1.697)	0.244		
Multi-visceral resection (presence)	0.502 (0.246–1.022)	0.128		
Postoperative complications (presence)	0.243 (0.130–1.002)	0.000	1.241 (0.867–2.991)	0.112
Adjuvant therapy (presence)	3.461 (0.480–6.952)	0.000	6.206 (0.852–10.199)	0.072
Tumor location				
Gastric cardia	Reference group			
Gastric fundus	1.452 (0.604–3.744)	0.965		
Gastric body	1.375 (0.407–4.651)	0.608		
Gastric antrum	1.913 (0.578–6.328)	0.288		
Tumor size				
≤ 2 cm	Reference group			
> 2–5 cm	0.101 (0.039–0.266)	0.004		
> 5–10 cm	0.172 (0.090–0.328)	0.000		
> 10 cm	0.446 (0.255–0.778)	0.000		
Mitotic count				
≤ 5/50HPF	Reference group			
> 5–10/50HPF	0.152 (0.083–0.277)	0.012		
> 10/50HPF	0.765 (0.417–1.402)	0.000		
Tumor necrosis (presence)	0.289 (0.169–0.495)	0.000	1.526 (0.875–2.661)	0.136
Modified NIH risk categories				
Very low-risk	Reference group			
Low-risk	0.000 (0.000–0.224)	0.928	0.000 (0.000–0.428)	0.924
Intermediate-risk	0.094 (0.040–0.221)	0.001	0.057 (0.017–0.187)	0.000
High-risk	0.395 (0.227–0.689)	0.000	0.279 (0.146–0.535)	0.000

Adjuvant therapy is postoperative imatinib treatment. Imatinib is only required for intermediate-risk and high-risk cases defined by modified NIH risk categories

category was an independent prognostic factor that affected DFS, which is consistent with previous findings.[22,23]

This study has some limitations. First, it is a retrospective study. Second, the details of the postoperative adjuvant therapy were unavailable. Multicenter randomized controlled studies should therefore *be performed to confirm the benefit of adjuvant therapy for elderly patients versus* young patients with gGISTs who are undergoing curative-intent resection.

Conclusion

Surgical resection remains the predominant treatment method for elderly patients with primary localized gGISTs. Elderly patients with gGISTs in our study had more comorbidities and postoperative complications than did younger patients. The proportion of elderly patients who received imatinib adjuvant therapy was lower than that of younger patients, and their prognosis was worse.

Methods to develop a standardized treatment model for elderly patients with gGISTs and to improve the proportions of patients who undergo adjuvant therapy and prognosis are still major clinical research topics.

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Author Contributions All authors listed above have made substantial contributions to the conception and design of this study, have revised its intellectual content, and have approved the final submitted version of the manuscript.

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Compliance with Ethical Standards

We received ethics approval for this case series from 10 medical centers in China (Guangdong General Hospital; Guangdong Academy of Medical Science, Guangzhou, People's Republic of China; Union Hospital Tongji Medical College Huazhong University of Science and Technology, Wuhan, People's Republic of China; Southern Medical University Nanfang Hospital, Guangzhou, People's Republic of China; Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center of Cancer Medicine, Guangzhou, People's Republic of China; Fujian Medical University Union Hospital, Fuzhou, People's Republic of China; Fudan University Shanghai Cancer Center, Shanghai, People's Republic of China; West China Hospital, Sichuan University, Chengdu, People's Republic of China; Peking University Cancer Hospital and Institute, Beijing, People's Republic of China; Liaoning Cancer Hospital and Institute, Shenyang, People's Republic of China; People's Liberation Army Cancer Center; 81st Hospital of PLA, Nanjing, People's Republic of China).

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Ma GL, Murphy JD, Martinez ME, Sicklick JK (2015) Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 24:298–302
2. Navarrete A, Momblan D, Almenara R, Lacy A (2017) Giant Gastric Gastrointestinal Stromal Tumor (GIST). Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 21:202–204
3. Soreide K, Sandvik OM, Soreide JA, Giljaca V, Jureckova A, Bulusu VR (2016) Global epidemiology of gastrointestinal stromal tumours (GIST): A systematic review of population-based cohort studies. Cancer epidemiology 40:39–46
4. Le Saux O, Falandry C, Gan HK, You B, Freyer G, Peron J (2016) Inclusion of elderly patients in oncology clinical trials. Annals of Oncology: Official Journal of the European Society for Medical Oncology 27:1799–1804
5. Farag S, van Coevorden F, Sneekes E, Grunhagen DJ, Reyners AKL, Boonstra PA, van der Graaf WT, Gelderlyblom HJ, Steeghs N (2017) Elderly patients with gastrointestinal stromal tumour (GIST) receive less treatment irrespective of performance score or comorbidity—A retrospective multicentre study in a large cohort of GIST patients. European journal of cancer 86:318–325
6. von Mehren M, Randall RL, Benjamin RS, Boles S, Bui MM, Conrad EU, 3rd, Ganjoo KN, George S, Gonzalez RJ, Heslin MJ, Kane JM, 3rd, Koon H, Mayerson J, McCarter M, McGarry SV, Meyer C, O'Donnell RJ, Pappo AS, Paz IB, Petersen IA, Pfeifer JD, Riedel RF, Schuetze S, Schupak KD, Schwartz HS, Tap WD, Wayne JD, Bergman MA, Scavone J (2016) Soft Tissue Sarcoma, Version 2.2016, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network : JNCCN 14:758–786
7. Muenst S, Thies S, Went P, Tornillo L, Bihl MP, Dirnhofer S (2011) Frequency, phenotype, and genotype of minute gastrointestinal stromal tumors in the stomach: an autopsy study. Human pathology 42:1849–1854
8. Kramer K, Knippschild U, Mayer B, Bogelspacher K, Spatz H, Henne-Bruns D, Agaimy A, Schwab M, Schmieder M (2015) Impact of age and gender on tumor related prognosis in gastrointestinal stromal tumors (GIST). BMC cancer 15:57
9. Mucciarini C, Rossi G, Bertolini F, Valli R, Cirilli C, Rashid I, Marcheselli L, Luppi G, Federico M (2007) Incidence and clinicopathologic features of gastrointestinal stromal tumors. A population-based study. BMC cancer 7:230
10. Dematteo RP, Ballman KV, Antonescu CR, Maki RG, Pisters PW, Demetri GD, Blackstein ME, Blanke CD, von Mehren M, Brennan MF, Patel S, McCarter MD, Polikoff JA, Tan BR, Owzar K, American College of Surgeons Oncology Group Intergroup Adjuvant GST (2009) Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 373:1097–1104
11. Joensuu H, Eriksson M, Sundby Hall K, Hartmann JT, Pink D, Schutte J, Ramadori G, Hohenberger P, Duyster J, Al-Batran SE, Schlemmer M, Bauer S, Wardelmann E, Sarlomo-Rikala M, Nilsson B, Sihto H, Monge OR, Bono P, Kallio R, Vehtari A, Leinonen M, Alvegard T, Reichardt P (2012) One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. Jama 307:1265–1272
12. Milone M, Elmore U, Vignali A, Mellano A, Gennarelli N, Manigrasso M, Milone F, De Palma GD, Muratore A, Rosati R (2017) Pulmonary Complications after Surgery for Rectal Cancer in Elderly Patients: Evaluation of Laparoscopic versus Open Approach from a Multicenter Study on 477 Consecutive Cases. Gastroenterology research and practice 2017:5893890
13. Yamano T, Yamauchi S, Kimura K, Babaya A, Hamanaka M, Kobayashi M, Fukumoto M, Tsukamoto K, Noda M, Tomita N, Sugihara K, Japanese Study Group for Postoperative Follow-up of Colorectal C (2017) Influence of age and comorbidity on prognosis and application of adjuvant chemotherapy in elderly Japanese patients with colorectal cancer: A retrospective multicentre study. European journal of cancer 81:90–101
14. Antoniou SA, Antoniou GA, Koch OO, Pointner R, Granderath FA (2015) Laparoscopic colorectal surgery confers lower mortality in the elderly: a systematic review and meta-analysis of 66,483 patients. Surgical endoscopy 29:322–333
15. Fujii S, Tsukamoto M, Fukushima Y, Shimada R, Okamoto K, Tsuchiya T, Nozawa K, Matsuda K, Hashiguchi Y (2016)

Systematic review of laparoscopic vs open surgery for colorectal cancer in elderly patients. World journal of gastrointestinal oncology 8:573–582

16. Harlan LC, Eisenstein J, Russell MC, Stevens JL, Cardona K (2015) Gastrointestinal stromal tumors: treatment patterns of a population-based sample. Journal of surgical oncology 111:702–707
17. Conley AP, Guerin A, Sasane M, Gauthier G, Schwiep F, Keir CH, Wu EQ (2014) Treatment patterns, prescribing decision drivers, and predictors of complete response following disease recurrence in gastrointestinal stromal tumor patients—a chart extract-based approach. Journal of gastrointestinal cancer 45:431–440
18. Sengupta S, Lohse CM, Leibovich BC, Frank I, Thompson RH, Webster WS, Zincke H, Blute ML, Cheville JC, Kwon ED (2005) Histologic coagulative tumor necrosis as a prognostic indicator of renal cell carcinoma aggressiveness. Cancer 104:511–520
19. Liu X, Qiu H, Zhang P, Feng X, Chen T, Li Y, Tao K, Li G, Sun X, Zhou Z, China Gastrointestinal Stromal Tumor Study G (2017) Prognostic role of tumor necrosis in patients undergoing curative intent resection for gastric gastrointestinal stromal tumor: a multicenter analysis of 740 cases in China. Cancer medicine
20. Hiraoka N, Ino Y, Sekine S, Tsuda H, Shimada K, Kosuge T, Zavada J, Yoshida M, Yamada K, Koyama T, Kanai Y (2010) Tumour necrosis is a postoperative prognostic marker for pancreatic cancer patients with a high interobserver reproducibility in histological evaluation. British journal of cancer 103:1057–1065
21. Cho MY, Sohn JH, Kim JM, Kim KM, Park YS, Kim WH, Jung JS, Jung ES, Jin SY, Kang DY, Park JB, Park HS, Choi YD, Sung SH, Kim YB, Kim H, Bae YK, Kang M, Chang HJ, Chae YS, Lee HE, Park DY, Lee YS, Kang YK, Kim HK, Chang HK, Hong SW, Choi YH, Shin O, Gu M, Kim YW, Kim GI, Chang SJ (2010) Current trends in the epidemiological and pathological characteristics of gastrointestinal stromal tumors in Korea, 2003-2004. Journal of Korean medical science 25:853–862
22. Kapoor R, Khosla D, Kumar P, Kumar N, Bera A (2013) Five-year follow up of patients with gastrointestinal stromal tumor: recurrence-free survival by risk group. Asia-Pacific journal of clinical oncology 9:40–46
23. Yin Z, Gao J, Liu W, Huang C, Shuai X, Wang G, Tao K, Zhang P (2017) Clinicopathological and Prognostic Analysis of Primary Gastrointestinal Stromal Tumor Presenting with Gastrointestinal Bleeding: a 10-Year Retrospective Study. Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract 21:792–800