Supplementary

Table S1 Proportion of elderly population (≥60 years) treated with regorafenib monotherapy originating from each center (n=203)

Center	N (%)
Beijing Hospital	14 (6.90)
The Affiliated Hospital of Hebei University	2 (0.99)
The Fourth Hospital of Hebei Medical University	13 (6.40)
Henan Cancer Hospital	27 (13.30)
Jiangsu Cancer Hospital	29 (14.28)
The Affiliated Hospital of Qingdao University	29 (14.28)
Shandong Tumor Hospital	11 (5.42)
Tianjin People's Hospital	10 (4.93)
Cancer Hospital of Chinese Academy of Medical Sciences	57 (28.08)
The First Hospital of China Medical University	11 (5.42)

Table S2 Differential analysis of baseline characteristics in patients receiving different initial daily doses

Characteristic	Subgroup	Initial daily dose, n (%)				P value
		40 mg (n=5)	80 mg (n=76)	120 mg (n=43)	160 mg (n=46)	
Sex	Male	3 (60.00)	54 (71.05)	36 (83.72)	33 (71.74)	0.38
	Female	2 (40.00)	22 (28.95)	7 (16.28)	13 (28.26)	
BMI (kg/m^2)	≥22	1 (50.00)	37 (69.81)	12 (54.55)	25 (71.43)	0.52
	<22	1 (50.00)	16 (30.19)	10 (45.45)	10 (28.57)	
ECOG score	0–1	5 (100.00)	74 (97.37)	39 (90.70)	42 (91.30)	0.35
	2–3	0 (0.00)	2 (2.63)	4 (9.30)	4 (8.70)	
Tumor location	Left	5 (100.00)	46 (74.19)	31 (91.18)	34 (89.47)	0.06
	Right	0 (0.00)	16 (25.81)	3 (8.82)	4 (10.53)	
Liver metastasis	Positive	2 (40.00)	46 (60.53)	22 (51.16)	23 (50.00)	0.55
	Negative	3 (60.00)	30 (39.47)	21 (48.84)	23 (50.00)	
Lung metastasis	Positive	4 (80.00)	41 (53.95)	29 (67.44)	29 (63.04)	0.37
	Negative	1 (20.00)	35 (46.05)	14 (32.56)	17 (36.96)	
RAS gene mutation status	Wild type	1 (50.00)	25 (50.00)	12 (50.00)	10 (43.48)	0.96
	Mutant	1 (50.00)	25 (50.00)	12 (50.00)	13 (56.52)	
BRAF gene mutation status	Wild type	3 (100.00)	34 (94.44)	19 (100.00)	16 (100.00)	0.54
	Mutant	0 (0.00)	2 (5.56)	0 (0.00)	0 (0.00)	
MMR gene status	dMMR	1 (33.33)	1 (2.50)	1 (4.76)	1 (4.76)	0.12
	pMMR	2 (66.67)	39 (97.50)	20 (95.24)	20 (95.24)	
Prior–anti VEGF therapy	Used	4 (80.00)	55 (74.32)	31 (72.09)	32 (69.57)	0.93
	Not used	1 (20.00)	19 (25.68)	12 (27.91)	14 (30.43)	

We defined factors with P<0.05 as significant. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; RAS, Rat sarcoma; BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; MMR, mismatch repair; dMMR, deficiency of MMR; pMMR, proficiency of MMR; VEGF, vascular endothelial growth factor.

https://dx.doi.org/10.21037/jgo-24-464

Table S3 Differential analysis of baseline characteristics in patients receiving different final daily doses

Characteristic	Subgroup	Final daily dose, n (%)			P value
		80 mg (n=51)	120 mg (n=37)	160 mg (n=28)	
Sex	Male	32 (62.75)	32 (86.49)	20 (71.43)	0.049
	Female	19 (37.25)	5 (13.51)	8 (28.57)	
BMI (kg/m^2)	≥22	24 (63.16)	13 (65.00)	15 (78.95)	0.47
	<22	14 (36.84)	7 (35.00)	4 (21.05)	
ECOG score	0–1	49 (96.08)	35 (94.59)	25 (89.29)	0.47
	2–3	2 (3.92)	2 (5.41)	3 (10.71)	
Tumor location	Left	30 (73.17)	29 (90.62)	22 (91.67)	0.07
	Right	11 (26.83)	3 (9.38)	2 (8.33)	
Liver metastasis	Positive	32 (62.75)	18 (48.65)	19 (67.86)	0.24
	Negative	19 (37.25)	19 (51.35)	9 (32.14)	
Lung metastasis	Positive	32 (62.75)	23 (62.16)	20 (71.43)	0.69
	Negative	19 (37.25)	14 (37.84)	8 (28.57)	
RAS gene mutation status	Wild type	17 (48.57)	9 (40.91)	7 (41.18)	0.81
	Mutant	18 (51.43)	13 (59.09)	10 (58.82)	
BRAF gene mutation status	Wild type	22 (91.67)	15 (100.00)	14 (100.00)	0.29
	Mutant	2 (8.33)	0 (0.00)	0 (0.00)	
MMR gene status	dMMR	1 (4.35)	2 (12.50)	0 (0.00)	0.29
	pMMR	22 (95.65)	14 (87.50)	16 (100.00)	
Prior–anti VEGF therapy	Used	41 (80.39)	25 (67.57)	20 (71.43)	0.37
	Not used	10 (19.61)	12 (32.43)	8 (28.57)	

We defined factors with P<0.05 as significant. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; RAS, Rat sarcoma; BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; MMR, mismatch repair; dMMR, deficiency of MMR; pMMR, proficiency of MMR; VEGF, vascular endothelial growth factor.

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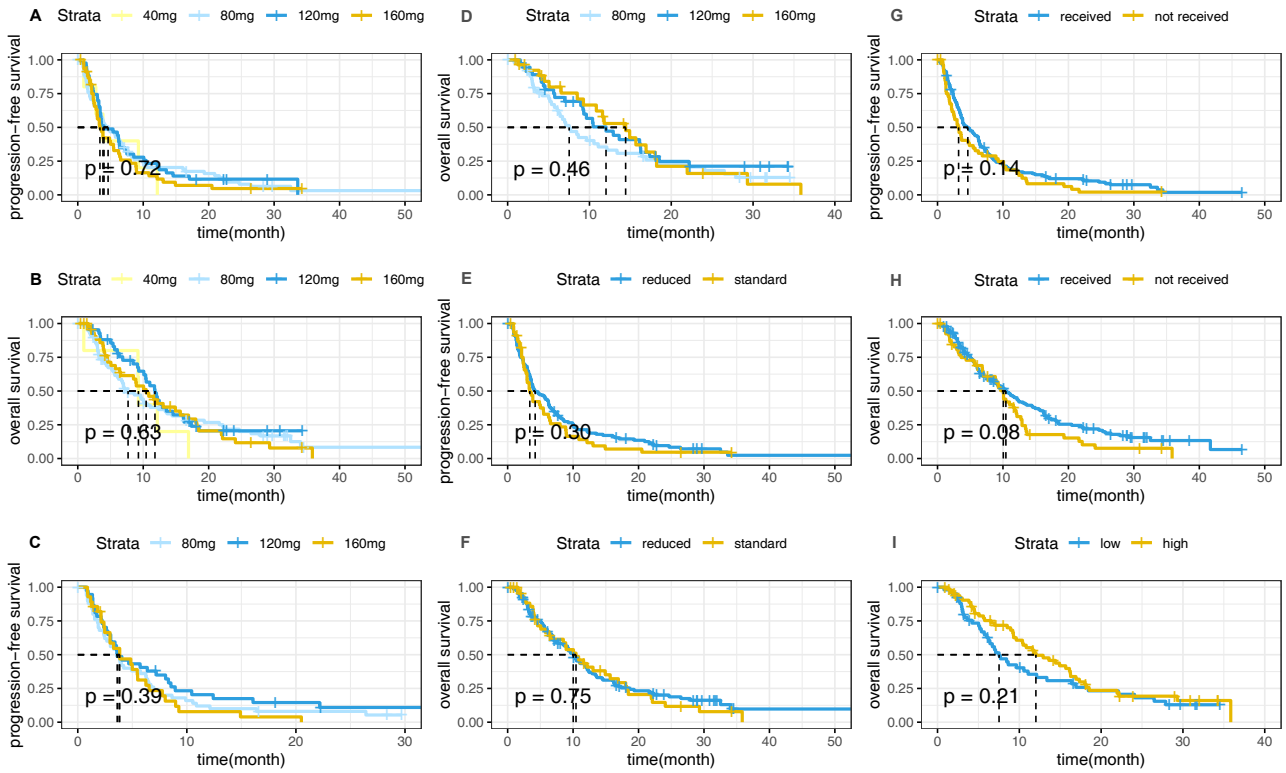

Figure S1 Survival analysis of elderly population (≥60 years) treated with regorafenib monotherapy after grouping by medication characteristics. (A,B) Grouped by initial daily dose. (C,D) Grouped by final daily dose. (E,F) Grouped into standard-dose and reduced-dose groups by initial daily dose. (G,H) Grouped by whether or not they had been treated with anti-VEGF therapy. (I) Grouped into high- and low-dose groups by final daily dose. VEGF, vascular endothelial growth factor.

https://dx.doi.org/10.21037/jgo-24-464

Table S4 Univariate and multivariate analyses of PFS in elderly population (≥60 years) treated with regorafenib monotherapy

Subgroup	N (%)	Univariate analysis		Multivariate analysis					
				Final daily dose-Model 1		Final daily dose-Model 2		Initial daily dose	
		HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Sex									
Male	152 (74.88)	1				1			
Female	51 (25.12)	0.87 (0.62–1.22)	0.43			1.04 (0.61–1.79)	0.88		
BMI (kg/m^2)									
≥22	85 (65.89)	1							
<22	44 (34.11)	1.00 (0.68–1.46)	0.98						
ECOG score									
0–1	190 (93.60)	1							
2–3	13 (6.40)	1.01 (0.56–1.81)	0.98						
Tumor location									
Left	134 (82.21)	1		1		1		1	
Right	29 (17.79)	0.74 (0.48–1.15)	0.18	0.72 (0.37–1.38)	0.32	0.71 (0.36–1.40)	0.34	0.96 (0.57–1.62)	0.87
Liver metastasis									
Positive	103 (50.74)	1		1		1		1	
Negative	100 (49.26)	0.79 (0.59–1.06)	0.11	1.09 (0.69–1.72)	0.70	1.09 (0.69–1.72)	0.72	0.94 (0.66–1.35)	0.75
Lung metastasis									
Positive	118 (58.13)	1		1		1		1	
Negative	85 (41.87)	0.63 (0.47–0.85)	0.002	0.56 (0.35–0.88)	0.01	0.55 (0.35–0.88)	0.01	0.63 (0.43–0.92)	0.02
RAS gene mutation status									
Wild type	59 (51.30)	1							
Mutant	56 (48.70)	1.01 (0.69–1.49)	0.95						
BRAF gene mutation status									
Wild type	81 (96.43)	1							
Mutant	3 (3.57)	0.74 (0.23–2.38)	0.62						
MMR gene status									
dMMR	5 (5.10)	1							
pMMR	93 (94.90)	1.21 (0.48–3.04)	0.69						
Prior–anti VEGF therapy									
Used	146 (73.00)	1		1		1		1	
Not used	54 (27.00)	1.28 (0.92–1.77)	0.14	1.11 (0.67–1.83)	0.70	1.11 (0.67–1.86)	0.68	1.03 (0.68–1.56)	0.88
Final daily dose									
160 mg	28 (24.14)	1		1		1			
120 mg	37 (31.90)	0.71 (0.42–1.19)	0.19	0.71 (0.40–1.27)	0.25	0.72 (0.40–1.30)	0.27		
80 mg	51 (43.96)	0.90 (0.56–1.46)	0.67	1.15 (0.66–2.02)	0.63	1.15 (0.65–2.01)	0.64		
Initial daily dose									
160 mg	46 (27.06)	1						1	
120 mg	43 (25.29)	0.80 (0.51–1.23)	0.31					0.76 (0.46–1.24)	0.27
80 mg	76 (44.71)	0.83 (0.57–1.23)	0.36					0.99 (0.64–1.54)	0.97
40 mg	5 (2.94)	1.02 (0.40–2.59)	0.96					0.93 (0.36–2.41)	0.88

We initially identified the variables associated with outcomes (P<0.20) through a univariate analysis. Variables with a P value <0.20 in the univariate analysis were adjusted in the Model 1. Variables with a P value <0.20 in the univariate analysis and those with a P value <0.05 from the differential analysis were adjusted in the Model 2. PFS, progression-free survival; BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; RAS, Rat sarcoma; BRAF, V-Raf Murine Sarcoma Viral Oncogene Homolog B; MMR, mismatch repair; dMMR, deficiency of MMR; pMMR, proficiency of MMR; VEGF, vascular endothelial growth factor; HR, hazard ratio; 95% CI, 95% confidence interval.

https://dx.doi.org/10.21037/jgo-24-464

Table S5 Patient characteristics before and after PSM

Subgroup	Unmatched data				Matched data			
	Low dose (n=51) N (%)	High dose (n=65) N (%)	P value	SMD	Low dose (n=26) N (%)	High dose (n=26) N (%)	P value	SMD
Lung metastasis			0.85	0.07			>0.99	<0.001
Positive	32 (62.75)	43 (66.15)			16 (61.54)	16 (61.54)		
Negative	19 (37.25)	22 (33.85)			10 (38.46)	10 (38.46)		
Sex			0.06	0.39			>0.99	<0.001
Male	32 (62.75)	52 (80.00)			19 (73.08)	19 (73.08)		
Female	19 (37.25)	13 (20.00)			7 (26.92)	7 (26.92)		
RAS gene mutation status			0.68	0.15			>0.99	<0.001
Wild type	17 (48.57)	16 (41.03)			12 (46.15)	12 (46.15)		
Mutant	18 (51.43)	23 (58.97)			14 (53.85)	14 (53.85)		
Prior anti-VEGF therapy			0.25	0.26			>0.99	<0.001
Used	41 (80.39)	45 (69.23)			20 (76.92)	20 (76.92)		
Not used	10 (19.61)	20 (30.77)			6 (23.08)	6 (23.08)		

PSM, propensity score matching; SMD, standardized mean difference; RAS, Rat sarcoma; VEGF, vascular endothelial growth factor.

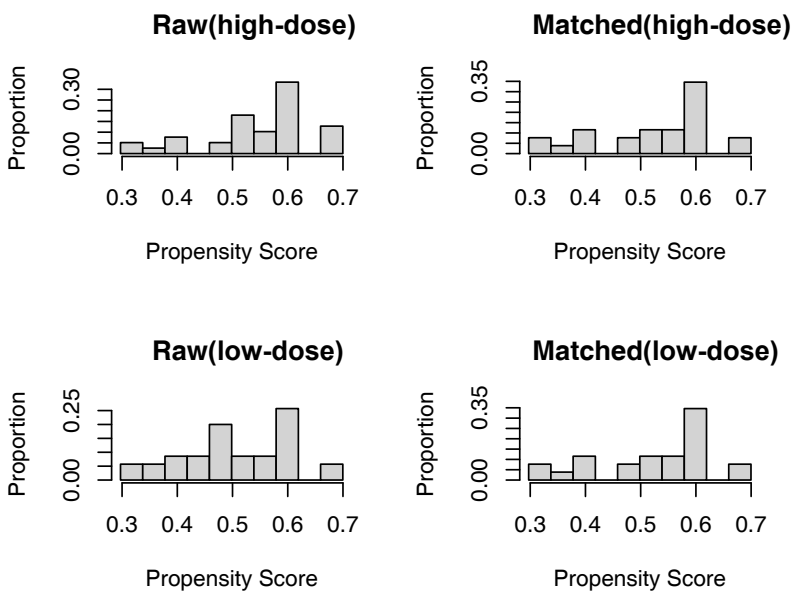

Figure S2 Histogram of propensity score for the final daily dose groups before and after PSM. PSM, propensity score matching.

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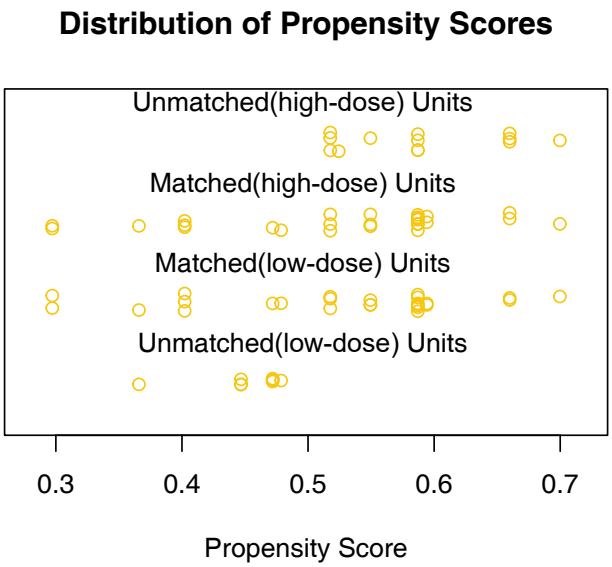

Figure S3 Jitter plot of propensity score for the final daily dose groups before and after PSM. PSM, propensity score matching.

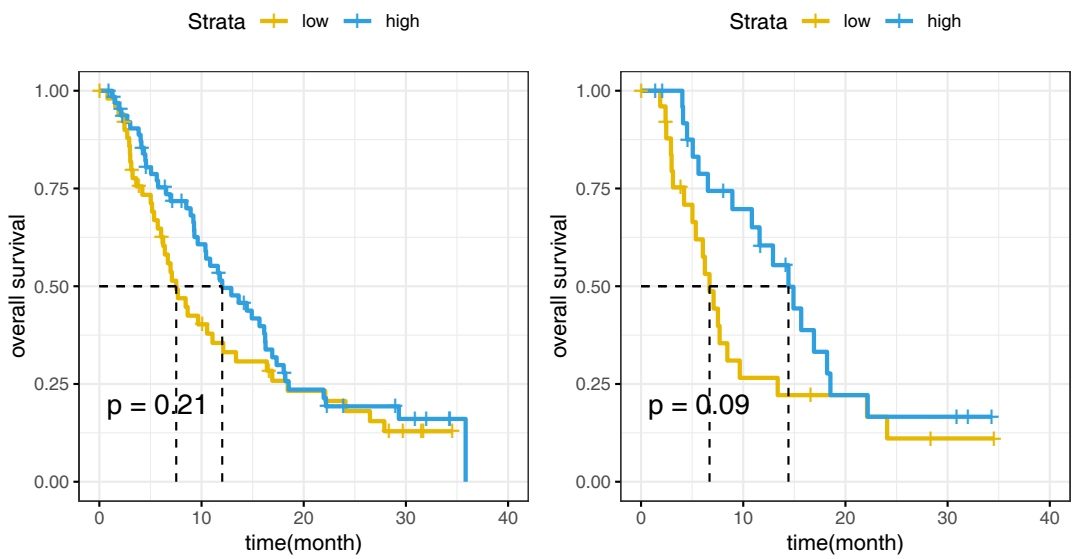

Figure S4 Survival analysis before and after PSM with final daily dose divided into high- and low-dose groups. (A) Before matching. (B) After matching. PSM, propensity score matching.

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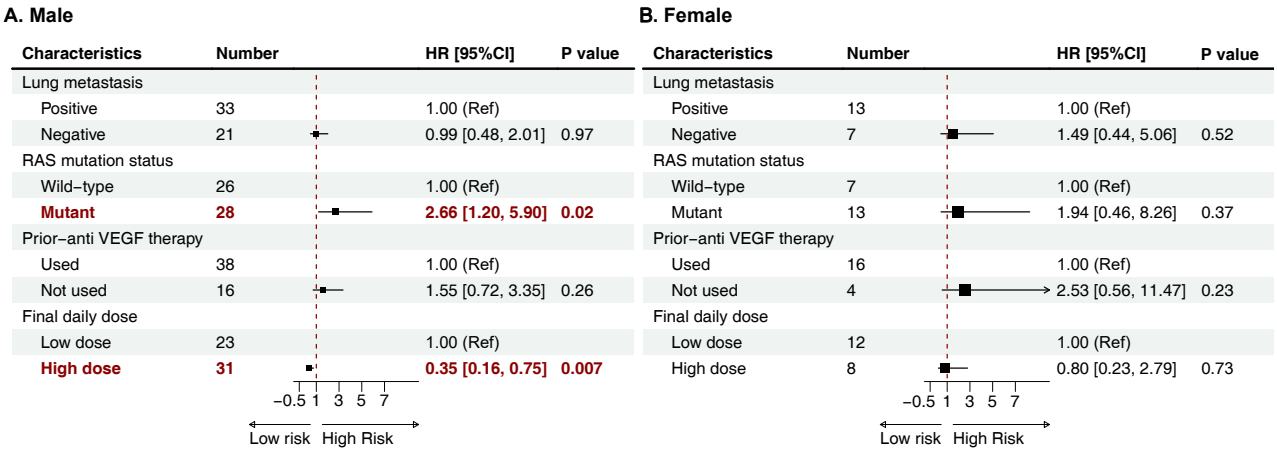

Figure S5 Results of Cox multivariate analysis for overall survival in elderly patients treated with regorafenib monotherapy, stratified by sex, in relation to the final daily dose. (A) Male. (B) Female. RAS, Rat sarcoma; VEGF, vascular endothelial growth factor; HR, hazard ratio; Ref, reference; 95% CI, 95% confidence interval.

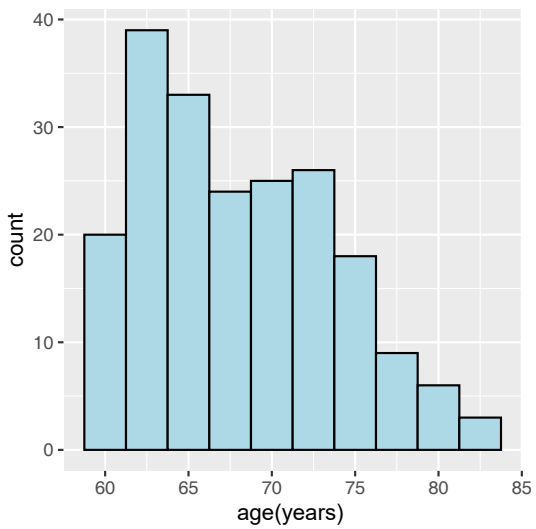

Figure S6 Age distribution of the elderly population (≥60 years) treated with regorafenib monotherapy.

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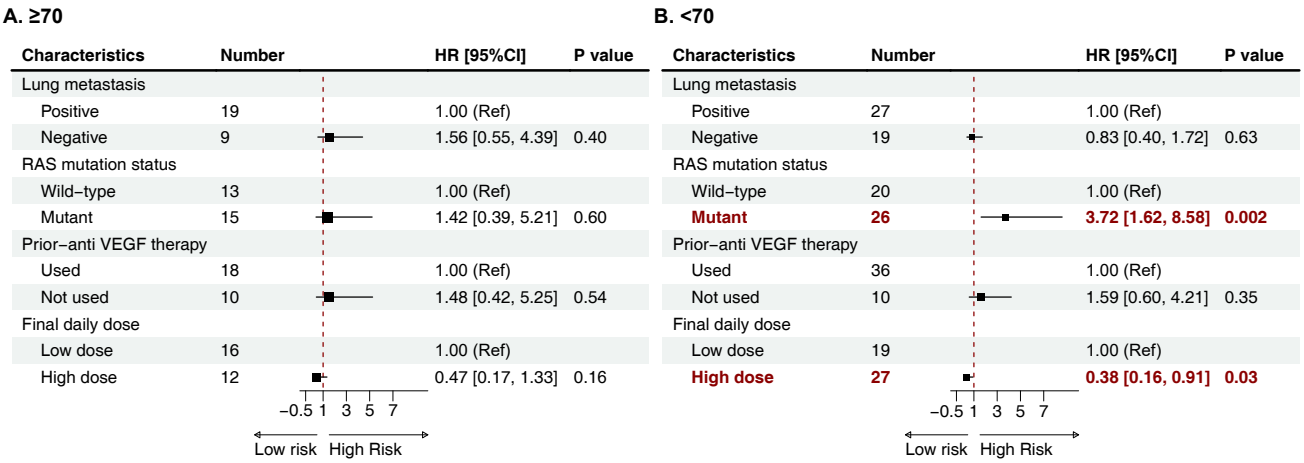

Figure S7 Results of Cox multivariate analysis for overall survival in elderly patients treated with regorafenib monotherapy, stratified by age (cut-off value: 70 years), in relation to the final daily dose. (A) ≥70. (B) <70. RAS, Rat sarcoma; VEGF, vascular endothelial growth factor; HR, hazard ratio; Ref, reference; 95% CI, 95% confidence interval.

Table S6 Characterization of adverse events in the elderly population (six centers*, n=77)

Characteristic	Subgroup	N (%)
Grade of adverse events	No adverse events	41 (53.25)
	Grade I	15 (19.48)
	Grade II	12 (15.58)
	Grade III	9 (11.69)
Adverse events	Fatigue	14 (18.18)
	Loss of appetite	14 (18.18)
	Hands and feet skin reactions (HFRS)	8 (10.39)
	Hypertension	6 (7.79)
	Diarrhea	6 (7.79)
	Liver damage	5 (6.49)
	Fever	4 (5.19)
	Hemorrhage	3 (3.90)

*Six centers: Beijing Hospital, The Affiliated Hospital of Hebei University, The Fourth Hospital of Hebei Medical University, Henan Cancer Hospital, Shandong Tumor Hospital and Tianjin People's Hospital.

https://dx.doi.org/10.21037/jgo-24-464

Table S7 Differential analysis of adverse events with baseline characteristics and dose of medication in elderly population (≥60 years) treated with regorafenib monotherapy

Characteristic	Subgroup	No adverse events (n=41), N (%)	Adverse event (n=36), N (%)	P value
Sex	Male	29 (70.73)	25 (69.44)	1.00
	Female	12 (29.27)	11 (30.56)	
Age (years)	≥70	12 (29.27)	15 (41.67)	0.37
	<70	29 (70.73)	21 (58.33)	
BMI (kg/m^2)	≥22	12 (75.00)	13 (72.22)	1.00
	<22	4 (25.00)	5 (27.78)	
ECOG score	0/1	38 (92.68)	34 (94.44)	1.00
	2/3	3 (7.32)	2 (5.56)	
Final daily dose	80 mg	10 (62.50)	6 (31.58)	0.14
	120–160 mg	6 (37.50)	13 (68.42)	
Initial daily dose	40–120 mg	26 (83.87)	18 (64.29)	0.15
	160 mg	5 (16.13)	10 (35.71)	

We defined factors with P<0.05 as significant. BMI, body mass index; ECOG, Eastern Cooperative Oncology Group.

https://dx.doi.org/10.21037/jgo-24-464