Comparative Analysis of Overall Survival and Cancer-Specific Survival Between Endoscopic Therapy and Surgical Resection for Gastrointestinal Stromal Tumors

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ABSTRACT

Background/Aims: *Few studies have compared endoscopic therapy (ET) with surgical resection for gastrointestinal stromal tumors (GISTs) measuring 2 to 10 cm in terms of overall survival and cancer-specific survival (CSS). This retrospective cohort study aimed to address this gap using data from the Surveillance, Epidemiology, and End Results (SEER) database.*

Materials and Methods: *Data were extracted from the SEER database for patients with GIST who underwent ET or surgical resection between 2007 and 2021. Survival differences were assessed using Kaplan–Meier curves and log-rank tests. Multivariable Cox proportional hazards models and 1 : 1 propensity score matching (propensity score matching [PSM], caliper = 0.02) were used to adjust for potential confounders.*

Results: *A total of 3471 patients (394 in the ET group and 3077 in the surgery group) were included. Before PSM, the 5- and 10-year overall survival (OS) rates were 84.11% (95% CI: 79.41%-89.10%) and 66.03% (95% CI: 57.96%-75.22%), respectively, in the ET group, compared with 86.00% (95% CI: 84.40%-87.70%) and 69.31% (95% CI: 66.15%-72.61%), respectively, in the surgery group. CSS showed similar patterns. After adjustment for confounders, ET was not significantly associated with OS (hazard ratios [HR] = 1.238, 95% CI: 0.934-1.639, P = .137) or CSS (HR = 0.932, 95% CI: 0.510-1.702, P = .818). PSM yielded comparable OS and CSS between the 2 treatment groups.*

Conclusion: *In a PSM cohort from the SEER database, ET was associated with overall survival and CSS comparable with that of surgical resection. However, these findings are hypothesis generating and require validation in prospective studies incorporating more detailed oncologic outcomes (R0 resection status, tumor rupture, recurrence, or adverse events, etc.). ET may be considered for carefully selected GISTs when performed by experienced endoscopists after thorough tumor assessment; however, these exploratory findings should not be interpreted as a treatment recommendation.*

Keywords: *Cancer-specific survival, endoscopic therapy, gastrointestinal stromal tumors, overall survival, surgical resection*

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract and are believed to arise from interstitial cells of Cajal or related stem-like progenitor cells.[1,2] Most GISTs are located in the stomach and small intestine.[2]

According to the clinical guidelines of the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN), gastric GISTs smaller than 2 cm without high-risk features can be safely managed with active surveillance, whereas nonmetastatic lesions 2 cm or larger generally warrant surgical resection.[3,4] Despite their inherent malignant potential, GISTs have an extremely low rate of lymph node metastasis, making endoscopic therapy (ET) an attractive and oncologically sound alternative.[3] Minimally invasive approaches have increasingly been adopted for the management of gastric and small intestinal GISTs, and ET has been shown to be safe and feasible for gastric GISTs up to 5 cm without compromising survival outcomes.[5,6]

Nonetheless, current NCCN guidelines do not recommend ET for GISTs larger than 5 cm, largely because of limited robust comparative evidence regarding its medium- and long-term safety profile in larger tumors.[3] Conversely, accumulating evidence suggests that ET for gastric GISTs larger than 5 cm is technically feasible and may offer favorable cost-effectiveness, better preservation of organ integrity and physiological function, faster

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postoperative recovery, and short-term outcomes comparable with those of laparoscopic resection.[7,8] In contemporary clinical practice, ET is increasingly performed in selected patients with gastric GISTs larger than 5 cm.

However, comparative studies evaluating survival outcomes after ET versus surgical resection for GISTs measuring 2 to 10 cm, particularly across different primary anatomical sites, are limited. The ESMO guidelines indicate that ET may be considered for small, low-risk GISTs at favorable anatomical sites after preoperative biopsy confirmation. Nevertheless, current guidelines recommend surgical resection as the standard treatment for large GISTs.[4] The present study was not intended to challenge this standard. Rather, using a large real-world database, this study aimed to compare overall survival and cancer-specific survival (CSS) between ET and surgical resection in patients with GISTs and to determine whether the findings were consistent across gastric and nongastric primary tumor sites. This hypothesis-generating analysis may inform future prospective studies.

MATERIALS AND METHODS

Study Design and Population

This retrospective analysis used data from the Surveillance, Epidemiology, and End Results (SEER) database (2007-2021) to compare survival after ET versus surgical resection for GISTs. The SEER program, maintained by the US National Cancer Institute (NCI), collects demographic, clinicopathologic, and treatment data from approximately 30% of the US population (https://seer.cancer.gov/). Because SEER is a publicly available, deidentified dataset, this study was exempt from institutional review board approval and informed consent.

Main Points

- *This population-based retrospective study compared overall survival and cancer-specific survival (CSS) between endoscopic therapy (ET) and surgical resection gastrointestinal stromal tumors (GISTs) measuring 2 to 10 cm using the Surveillance, Epidemiology, and End Results database.*
- *Both before and after 1 : 1 propensity score matching, overall survival and CSS were comparable between the ET and surgical resection groups.*
- *ET may be an option for carefully selected patients with GIST when performed by experienced endoscopists after thorough tumor assessment; however, these exploratory findings should not be interpreted as a treatment recommendation.*

Using SEER*Stat software (version 8.4.4; [National Cancer Institute; Bethesda, MD, USA]), patients aged 19 and older who were diagnosed with GIST between 2007 and 2021 were identified from the SEER database. According to the third edition of the International Classification of Diseases for Oncology, GIST is designated by histological code 8936. Patients were excluded if they met any of the following criteria: (1) unclear surgical method; (2) missing follow-up information or follow-up duration of less than 1 month; (3) tumor size less than 2 cm, greater than 10 cm, or unknown; (4) lymph node metastasis (N1); (5) distant metastasis (M1); (6) multiple primary cancers or nongastrointestinal GISTs; or (7) unknown tumor grade. Ultimately, 3471 patients were included in the study. A flowchart illustrating the screening process is presented in Figure 1.

Covariates and Outcomes

Patient data were obtained from the SEER database and included demographic characteristics such as age, sex, race, year of diagnosis, and marital status, as well as tumor characteristics including tumor size, primary site, T stage, N stage, M stage, and tumor grade. Data on chemotherapy, survival time, cause of death, and treatment methods were also collected. In this study, ET was defined as endoscopic local tumor excision or resection procedures for GIST, corresponding to SEER treatment codes 20-27. Surgical resection was defined according to SEER codes 30-80. Patients were stratified into 2 age groups: younger than 60 years and 60 years or older. Tumors were also categorized into 2 groups according to the median size: 20-46 mm and 47-100 mm. The primary endpoints were overall survival (OS) and CSS among patients with GIST who underwent endoscopic or surgical intervention. OS was calculated from the date of diagnosis to the date of death from any cause or the date of the last follow-up, whereas CSS was calculated from the date of diagnosis to the date of death from GIST or the date of the last follow-up.

Statistical Analysis

Patients were divided into 2 groups according to treatment: the ET group and the surgical resection group. For continuous variables, the *t*-test was used for between-group comparisons when the data met the assumptions of normality and homogeneity of variances; otherwise, the nonparametric Wilcoxon rank-sum test was used. For categorical data, either the chi-square test or Fisher's exact test was used. To mitigate selection bias and confounding, a 1 : 1 propensity score matching (PSM) was performed using a caliper

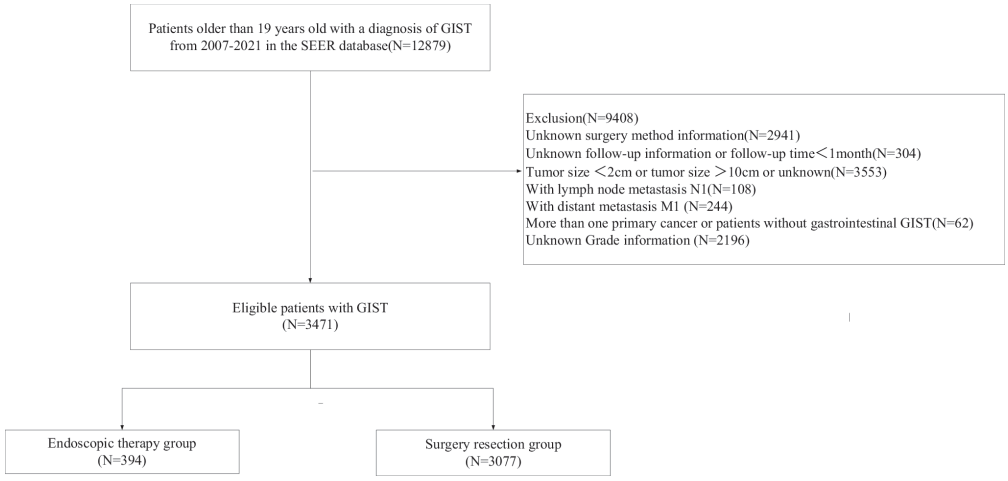

Figure 1. Flowchart of eligible patients with GISTs measuring 2 to 10 cm. GIST, gastrointestinal stromal tumors.

width of 0.02 to construct a cohort with balanced baseline characteristics between the 2 groups. Following PSM, the clinical and pathological characteristics of patients in the 2 groups were reassessed. The Kaplan–Meier method was used to estimate survival curves, and the log-rank test was used to compare survival between groups. Cox proportional hazards regression analysis was performed to identify predictors of survival, with adjustments for potential confounders. Hazard ratios (HRs) and 95% CIs were reported. Subgroup analyses stratified by primary tumor location (gastric vs. nongastric) were performed using the Kaplan–Meier and Cox regression methods before and after PSM. All statistical analyses were performed using R software (version 4.3.1; [R Foundation for Statistical Computing; Vienna, Austria]). The "survminer" and "survival" packages were used to generate survival curves, and the "MatchIt" package was used to perform PSM. All statistical tests were 2-tailed, and a *P* value <.05 was considered statistically significant. No artificial intelligence was used during the preparation of the manuscript.

RESULTS

Baseline Characteristics

Ultimately, 3471 patients with GIST were included in the final analysis. Table 1 summarizes the clinicopathological characteristics of the 2 groups. Of these, 394 patients received ET and 3077 cases underwent surgical resection. No significant differences were observed between the 2 groups in age, sex, race, year of diagnosis, marital status, tumor location, or pathological differentiation grade (all *P* > .05). Notably, the proportion of patients with tumor sizes ranging from 47 to 100 mm was significantly higher in the surgical resection group than in the ET group (48.39% vs. 35.79%, *P* < .001). The median tumor size was also larger in the surgical resection group than in the ET group (45 vs 40 mm; *P* < .001). Patients who underwent surgical resection were more likely to receive chemotherapy than those in the ET group (31.91% vs. 26.90%; *P* = .044). After PSM, no significant differences were observed between the 2 groups in age, sex, race, year of diagnosis, marital status, tumor location, tumor size, pathological differentiation grade, or receipt of chemotherapy.

Comparison of Endoscopic Therapy and Surgical Resection Outcomes

In this study, 57 deaths (14.47%) occurred in the ET group compared with 399 deaths (12.97%) in the surgical resection group. Of these, GIST-related deaths occurred in 12 patients in the ET group and 123 patients in the surgical resection group. The median follow-up time was 37.0 months (P_{25}, P75, 11.0-74.0 months) in the ET group and 38.0 months (P_{25}, P_{75}: 13.0, 74.0 months) in the surgical resection group, with no significant difference between the 2 groups (*P* = .675). The median survival time was not reached in either group. OS rates were comparable between the ET group (5-year OS: 84.11%, 95% CI: 79.41%-89.10%; 10-year OS: 66.03%, 95% CI: 57.96%-75.22%) and the surgical resection group (5-year OS: 86.00%, 95% CI: 84.40%-87.70%; 10-year OS: 69.31%, 95% CI: 66.15%-72.61%). Similarly, CSS rates were comparable between the ET group (5-year CSS: 95.95%, 95% CI: 93.13%-98.86%; 10-year CSS: 91.12%, 95% CI: 85.76%-96.81%) and the surgical resection group (5-year CSS: 95.00%, 95% CI: 94.00%-96.10%; 10-year CSS: 90.54%, 95% CI: 88.53%-92.60%). The survival curves for the 2 groups are shown in Figure 2.

Table 1. Comparison of Baseline Characteristics Between Endoscopic Therapy and Surgical Resection Groups in Patients with Gastric GIST Before and After PSM

	Before PSM				After PSM			
Characteristics	Endoscopic Therapy (n = 394)	Surgical Resection (n = 3077)	Statistic Value	*P*	Endoscopic Therapy (n = 394)	Surgical Resection (n = 394)	Statistic Value	*P*
Age, %			0.046	.83			0.282	.596
<60 years	133 (33.76)	1022 (33.21)			133 (33.76)	126 (31.98)		
≥60 years	261 (66.24)	2055 (66.79)			261 (66.24)	268 (68.02)		
Gender, %			1.272	.259			0.02	.886
Male	183 (46.45)	1522 (49.46)			183 (46.45)	185 (46.95)		
Female	211 (53.55)	1555 (50.54)			211 (53.55)	209 (53.05)		
Race, %			4.509	.105			0.157	.925
White	276 (70.05)	2017 (65.55)			276 (70.05)	281 (71.32)		
Black	58 (14.72)	584 (18.98)			58 (14.72)	56 (14.21)		
Other	60 (15.23)	476 (15.47)			60 (15.23)	57 (14.47)		
Year of diagnosis (%)			0.84	.657			1.098	.578
2007-2011	48 (12.18)	347 (11.28)			48 (12.18)	40 (10.15)		
2012-2016	108 (27.41)	907 (29.48)			108 (27.41)	104 (26.40)		
2017-2021	238 (60.41)	1823 (59.24)			238 (60.41)	250 (63.45)		
Marital status (%)			0.975	.614			0.075	.963
Married	242 (61.42)	1826 (59.34)			242 (61.42)	240 (60.91)		
Unmarried	137 (34.77)	1107 (35.98)			137 (34.77)	140 (35.53)		
Unknown	15 (3.81)	144 (4.68)			15 (3.81)	14 (3.56)		
Tumor site, %			0.198	.656			0.576	.448
Gastric	260 (65.99)	2065 (67.11)			260 (65.99)	270 (68.53)		
Nongastric	134 (34.01)	1012 (32.89)			134 (34.01)	124 (31.47)		
Tumor size (median [P_{25}, P_{75}])	40 (29.55)	45 (34.65)	−5.436	<.001	40 (29.55)	40 (30.55)	−1.197	.231
Tumor size, mm, %			22.279	<.001			0.006	.941
20-46 mm	253 (64.21)	1588 (51.61)			253 (64.21)	254 (64.47)		
47-100 mm	141 (35.79)	1489 (48.39)			141 (35.79)	140 (35.53)		
Grade, %			4.577	.206			0.957	.812
Well differentiated	282 (71.57)	2044 (66.43)			282 (71.57)	280 (71.07)		
Moderately differentiated	53 (13.45)	464 (15.08)			53 (13.45)	60 (15.23)		
Poorly differentiated	11 (2.79)	121 (3.93)			11 (2.79)	8 (2.03)		
Undifferentiated	48 (12.19)	448 (14.56)			48 (12.19)	46 (11.67)		
Chemotherapy, %			4.075	.044			1.136	.286
Yes	106 (26.90)	982 (31.91)			106 (26.90)	93 (23.60)		
No	288 (73.10)	2095 (68.09)			288 (73.10)	301 (76.40)		

GIST, gastrointestinal stromal tumors; PSM, propensity score matching.

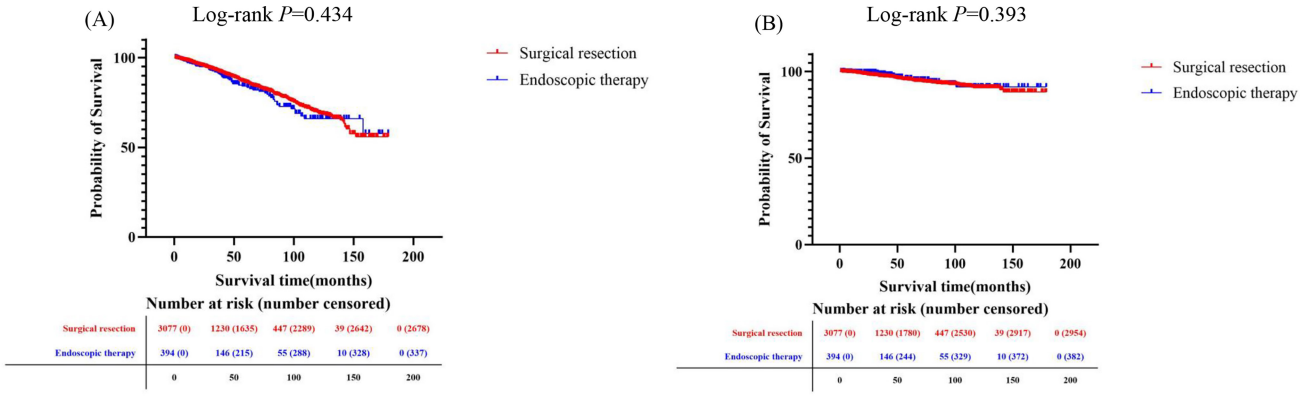

Figure 2. Kaplan–Meier curves for overall survival and cancer-specific survival according to treatment method before PSM. (A) Overall survival and (B) cancer-specific survival. Beyond 150 months, the number of patients at risk was too small to provide reliable estimates. PSM, propensity score matching.

Prediction Results of the Multivariable Cox Regression Analysis

The results of the multivariable Cox proportional hazards regression analysis are summarized in Table 2. No significant differences in OS (HR = 1.238, 95% CI: 0.934-1.639, *P* = .137) or CSS (HR = 0.932, 95% CI: 0.510-1.702, *P* = .818) were observed between the ET and surgical resection groups. Older age (≥60 years), male sex, tumor size ≥47 mm, nongastric tumor location, and poor or undifferentiated tumor grade were associated with worse OS or CSS. In addition, patients who did not receive chemotherapy had worse OS. Race was not significantly associated with OS or CSS.

Comparison of Survival Outcomes Between Endoscopic Therapy and Surgical Resection After Propensity Score Matching

Following PSM, a cohort of 788 patients was established, comprising 394 patients in the ET group and 394 patients in the surgical resection group. As shown in Table 1, no significant differences in baseline characteristics were observed between the 2 groups. The distribution of propensity scores is shown in Supplementary Figure 1. The PSM histogram demonstrated a balanced distribution of patients between the 2 groups (Supplementary Figure 2). Following PSM, survival analyses and log-rank tests were performed to compare survival outcomes between the 2 groups. No significant differences in OS were observed between the ET and surgical resection groups at 5 years (84.11% [95% CI, 79.41%-89.10%] vs 89.37% [95% CI, 85.24%-93.71%]) or 10 years (66.03% [95% CI, 57.96%-75.22%] vs 68.88% [95% CI, 59.72%-79.44%]). Similarly, no significant differences in CSS were observed at 5 years (95.95% [95% CI, 93.13%-98.86%] vs 97.76% [95% CI, 95.79%-99.78%]) or 10 years (91.12% [95% CI, 85.76%-96.81%] vs 97.76% [95% CI, 95.79%-99.78%]). The survival curves for the 2 groups after PSM are shown in Figure 3. After PSM, a multivariate Cox proportional hazards regression analysis showed no significant differences between the surgical resection and ET groups in OS (HR = 1.344, 95% CI: 0.901-2.007, *P* = .148) or CSS (HR = 2.193, 95% CI: 0.739-6.502, *P* = .157). After adjustment for potential confounders, older age was independently associated with worse OS (HR, 3.162 [95% CI, 1.811-5.522]; *P* < .001) as was an undifferentiated tumor grade (HR, 2.174 [95% CI: 1.138-4.155]). Nongastric tumor location was independently associated with worse CSS (HR, 4.841 [95% CI, 1.399-16.758]) (Supplementary Table 1).

Subgroup Analysis by Primary Tumor Location

Stratified survival analyses were performed according to primary tumor site (gastric vs. nongastric) before and after PSM. Detailed results are presented in Supplementary Figures 3-6 and Supplementary Tables 2-4. In the gastric GIST subgroup, no significant differences in OS or CSS was observed between the ET and surgical resection groups before PSM, as demonstrated by log-rank tests (*P* = .537 and *P* = .182, respectively) and confirmed by multivariate Cox proportional hazards regression analysis (OS: HR, 1.276 [95% CI, 0.889-1.832]; *P* = .187; CSS: HR, 0.856 [95% CI, 0.306-2.398]; *P* = .767). After PSM, no significant difference in OS was observed between the surgical resection and ET groups (log-rank *P* = .141). For CSS, a borderline significant difference was observed between the 2 groups (log-rank *P* = .048, Supplementary Figure 4B). In the nongastric GIST subgroup, no significant differences in survival were observed between the 2 treatment groups in any analyses (all *P* > .05).

Table 2. Multivariate Cox Regression Analysis of OS and CSS in Patients Before PSM

	OS		CSS	
Characteristics	HR (95% CI)	*P*	HR (95% CI)	*P*
Therapeutic method				
Surgical resection	Reference		Reference	
Endoscopic therapy	1.238 (0.934, 1.639)	.137	0.932 (0.510, 1.702)	.818
Age				
<60 years	Reference		Reference	
≥60 years	3.671 (2.835, 4.752)	<.001	2.012 (1.361, 2.975)	<.001
Gender				
Male	Reference		Reference	
Female	0.583 (0.481, 0.707)	<.001	0.428 (0.296, 0.619)	<.001
Race		.089		.313
White	Reference		Reference	
Black	1.174 (0.924, 1.493)	.189	1.359 (0.869, 2.127)	.179
Other	0.798 (0.594, 1.071)	.133	0.890 (0.535, 1.481)	.654
Year of diagnosis		.015		<.001
2007-2011	Reference		Reference	
2012-2016	1.011 (0.803, 1.273)	.926	0.955 (0.645, 1.415)	.819
2017-2021	0.675 (0.490, 0.929)	.016	0.303 (0.164, 0.559)	<.001
Marital status		<.001		.186
Married	Reference		Reference	
Unmarried	1.587 (1.301, 1.936)	<.001	1.392 (0.962, 2.015)	.079
Unknown	1.153 (0.719, 1.848)	.554	0.880 (0.354, 2.190)	.784
Tumor site				
Gastric	Reference		Reference	
Nongastric	1.298 (1.065, 1.583)	.01	1.781 (1.246, 2.546)	.002
Tumor size				
20-46 mm	Reference		Reference	
47-100 mm	1.266 (1.042, 1.539)	.018	1.522 (1.036, 2.236)	.033
Grade (differentiated)		<.001		<.001
Well differentiated	Reference		Reference	
Moderately differentiated	1.174 (0.933, 1.477)	.172	2.088 (1.291, 3.379)	.003
Poorly differentiated	2.362 (1.731, 3.225)	<.001	5.388 (3.125, 9.288)	<.001
Undifferentiated	1.785 (1.336, 2.384)	<.001	5.264 (3.212, 8.627)	<.001
Chemotherapy				
Yes	Reference		Reference	
No	1.270 (1.026, 1.573)	.028	0.752 (0.522, 1.084)	.127

CSS, cancer-specific survival; OS, overall survival; PSM, propensity score matching.

DISCUSSION

The study found no significant differences in OS or CSS between patients with GISTs measuring 2-10 cm who underwent ET or surgical resection. At baseline, patients in the ET group had smaller tumors and were less likely to receive chemotherapy than those in the surgical resection

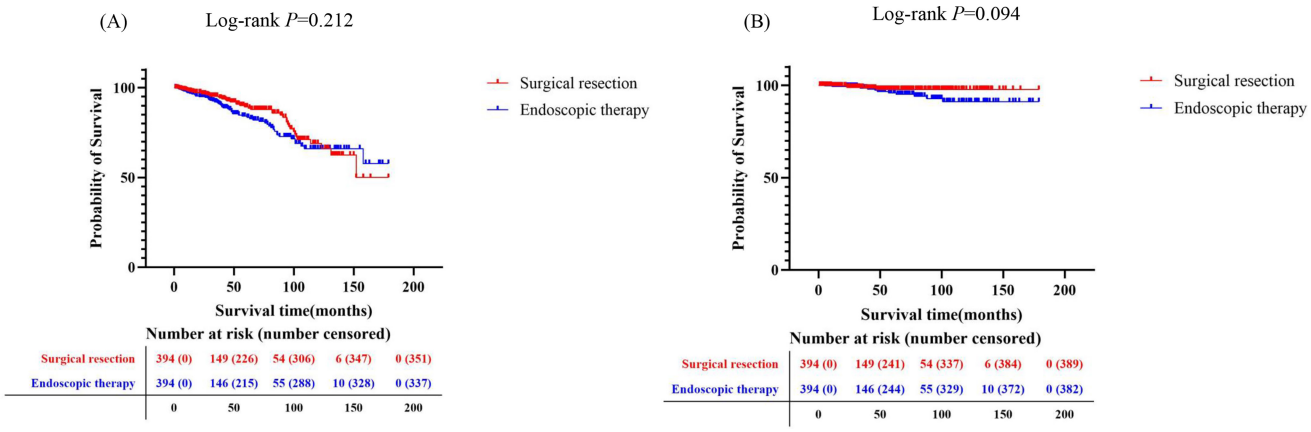

Figure 3. Kaplan–Meier curves for overall survival and cancer-specific survival according to treatment method after PSM. (A) Overall survival and (B) cancer-specific survival. Beyond 150 months, the number of patients at risk was too small to provide reliable estimates. PSM, propensity score matching.

group. After adjustment for potential confounders using multivariate Cox proportional hazards regression model, OS and CSS remained comparable between the 2 groups. Additionally, survival analysis following 1 : 1 PSM showed no significant differences in OS or CSS between the 2 treatment groups. This finding remained consistent after stratification by primary tumor location. In subgroup analyses of gastric and nongastric GISTs, ET and surgical resection were associated with comparable OS and CSS in multivariable Cox proportional hazards regression analyses before PSM, and no significant differences were observed after matching. The only exception was a borderline significant difference in CSS in the gastric subgroup, which was based on only 4 events and should therefore be interpreted with caution.

These findings are consistent with those of previous studies. Prior research demonstrated that, for gastric GISTs measuring 2-5 cm, survival outcomes with ET were comparable to those with surgical resection.[9] Liu et al[10] reported similar findings in patients with GISTs measuring 5 to 10 cm. Zhang et al[11] demonstrated that ET was technically feasible for gastric GISTs with a maximum diameter of 7 cm, particularly those with intraluminal and intraluminal–extraluminal growth types, with short-term outcomes comparable to those of laparoscopic surgery and advantages including faster postoperative recovery and lower costs. Furthermore, a single-center retrospective study included 23 patients with giant submucosal gastric tumors, 18 of whom had GISTs, who underwent ET without laparoscopic assistance. The mean tumor diameter was 6.4 ± 0.5 cm. Complete tumor resection was achieved in 22 patients (95.7%), and 4 patients developed complications that resolved with conservative treatment. No residual tumor or recurrence was observed during follow-up, suggesting that ET alone may be feasible for giant gastric GISTs.[12] Thus, by including a large cohort of patients with GISTs measuring 2 to 10 cm, the present observational study provides additional real-world evidence that ET and surgical resection may have comparable OS.

However, these findings should be interpreted in the context of the substantial technical and oncologic challenges associated with ET of larger GISTs. In clinical practice, the key controversies regarding ET for large GISTs include the likelihood of complete tumor resection rate, risk of positive margins, and management of procedure-related complications. ET for larger GISTs carries specific technical and oncologic risks, including piecemeal resection, tumor seeding, incomplete resection with positive margins, and increased risks of perforation or bleeding.[13,14] Because of the deep infiltration and complex growth patterns of large GISTs, accurate assessment of tumor boundaries and depth of invasion can be challenging, potentially increasing the risk of positive margins. For large tumors located at anatomically challenging sites such as the gastric fundus or posterior wall, the limited endoscopic working space may further increase the risk of complications such as perforation and bleeding. In addition, retrieval of large resected specimens through natural orifices remains technically challenging. Accordingly, current guidelines do not recommend routine ET for GISTs larger than 5 cm.[3,4]

These technical and oncological risks cannot be assessed using the SEER registry. The SEER database does not capture whether tumor resection was performed en bloc or piecemeal, whether tumor seeding occurred, whether

margins were negative (R0), whether protective devices (e.g., endoscopic overtubes or retrieval bags) were used, or details regarding procedure-related adverse events such as perforation or bleeding. Consequently, the finding of comparable survival between ET and surgical resection should not be interpreted as a practice-changing recommendation. Rather, this exploratory comparative analysis generates the hypothesis that ET may provide OS and CSS comparable to those of surgical resection in carefully selected patients when performed by experienced endoscopists. Nevertheless, the SEER database cannot assess the adequacy of preoperative patient selection or the successful resolution of technical challenges encountered during endoscopic procedures.

Preoperative risk stratification with endoscopic ultrasound (EUS)–guided sampling is essential for assessing tumor size, growth pattern, mitotic index, and high-risk features, as recommended by 2022 ESMO guidelines.[4] ET for larger GISTs should be considered only in carefully selected patients after rigorous preoperative evaluation and performed by experienced endoscopists. Accordingly, management of large GISTs requires individualized assessment and precise therapeutic planning. Histopathologic findings and mitotic index values obtained through EUS-guided sampling directly inform tailored treatment selection. For tumors in readily accessible locations (e.g., the anterior wall of the gastric body), with predominantly intraluminal growth and without extensive adhesions, ET may be considered in carefully selected cases. However, such procedures should be performed by experienced endoscopists with adequate preparation for potential major complications such as significant bleeding or perforation. For tumors located in anatomically challenging sites, exhibiting exophytic growth, or suspected of invading adjacent organs, surgical resection remains the preferred approach. Laparoscopic and endoscopic cooperative surgery (LECS) represents a hybrid approach that may combine the advantages of both modalities; however, it increases procedural complexity, and large-scale prospective evidence regarding long-term outcomes in large GISTs remains limited.[15-20] Future, multicenter, prospective randomized controlled trials involving diverse international patient cohorts are needed to further establish the safety and efficacy of ET for large GISTs.

Limitations

Several important limitations should be acknowledged. First, the SEER database lacks critical information on R0 resection status, tumor rupture, local or distant recurrence, treatment-related adverse events (e.g., perforation, bleeding, and piecemeal resection), and operator experience. The SEER-based analysis cannot account for these technical variables, which is a limitation and should be addressed in future prospective registries. These missing variables may influence the observed survival equivalence; therefore, the findings should not be interpreted as a treatment recommendation. Second, GISTs are relatively rare. Although the SEER database provides data from 2007 to 2021 and includes 394 patients who underwent ET, the sample size remains relatively small and may limit the generalizability of the findings. Third, the retrospective nature of the SEER database precludes assessment of several clinically relevant parameters such as detailed complication rates, margin status, length of hospital stay, and specific technical details of the endoscopic and surgical procedures performed. Moreover, the SEER database lacks detailed information on chemotherapy regimens. The absence of comprehensive chemotherapy data may have influenced the survival outcomes observed in this study.[21] Future studies using databases with more comprehensive treatment information are needed to better elucidate the role of chemotherapy in combination with endoscopic or surgical interventions. Furthermore, although PSM and multivariate Cox regression analysis were used to adjust for known confounding variables, these methods cannot fully account for unmeasured confounders or biases inherent in the retrospective study design. For example, the choice between ET and surgery may have been influenced by factors such as tumor location, patient comorbidities, and the expertise of the treating physician none of which are fully captured in the SEER database. These unmeasured variables may have influenced the observed outcomes. In addition, the median follow-up duration was 37.0 months in the ET group and 38.0 months in the surgical resection group. Given that GIST recurrence and disease-related mortality may occur 5-10 years after surgical resection, the relatively short follow-up period in the present study may be insufficient to fully assess long-term prognostic outcomes. Therefore, the findings should be interpreted with caution. Further well-designed studies with longer follow-up and larger cohorts are warranted to comprehensively compare the long-term survival benefits and safety profiles of ET and surgical resection for GISTs across diverse patient populations.

CONCLUSION

In a propensity score–matched cohort from the SEER database, patients undergoing ET demonstrated comparable overall survival and CSS. However, the absence of critical procedural and oncologic variables in the SEER database limits the generalizability of these findings, which remain strictly hypothesis generating. Given the

technical challenges associated with en bloc resection for GISTs larger than 5 cm, the potential need for combined procedures, and the risk of tumor seeding with piecemeal resection, ET should be performed with caution. In principle, ET may be considered for carefully selected GISTs after thorough preoperative assessment of tumor characteristics and should be performed by experienced endoscopists. However, ET should not be routinely adopted without further prospective validation. Future prospective studies are warranted to optimize therapeutic strategies for GISTs and provide stronger evidence-based medical support.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Artificial Intelligence Usage Statement: The authors declared that no Artificial Intelligence tool was used in the preparation of the manuscript.

Ethics Committee Approval: N/A.

Informed Consent: N/A.

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Author Contributions: Concept – S.C.; Design – S.C., G.Q., Y.X., Q.Z.; Supervision – F.L., S.D.; Resources – ; Materials – S.C.; Data Collection and/or Processing – S.C.; Analysis and/or Interpretation – S.C.; Literature Search – S.C.; Writing – S.C.; Critical Review – G.Q., Y.X., Q.Z., F.L., S.D.

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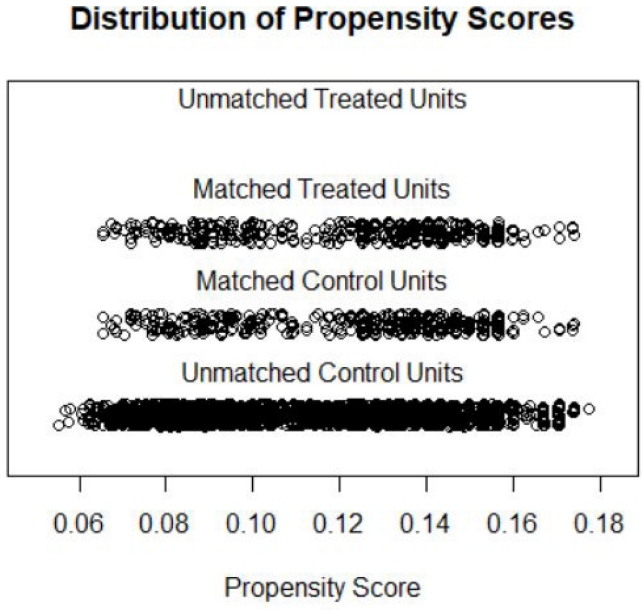
SUPPLEMENTARY INFORMATION

Stratified Subgroup Analyses by Primary Tumor Location

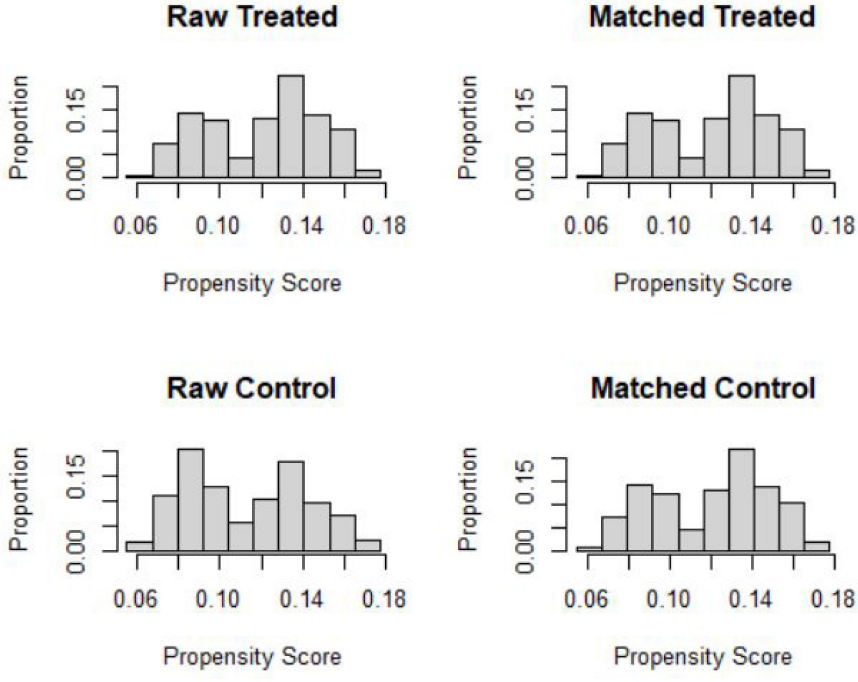
The authors have implemented stratified survival analyses for gastric and non-gastric GIST cohorts both before and after propensity score matching (PSM), including Kaplan–Meier log-rank tests and multivariate Cox proportional hazards regression models. All corresponding analytical results are supplemented as Supplementary Figures 3-6 and Supplementary Tables 2–4 in the revised manuscript, with detailed outcomes summarized below:

1. **Patients with gastric GISTs**
   - (1.1) **Before PSM**
   - Kaplan–Meier log-rank tests revealed no significant differences between surgical resection and endoscopic therapy for overall survival (OS, log-rank *P* = .537, Supplementary Figure 3A) or cancer-specific survival (CSS, log-rank *P* = .182, Supplementary Table Figure 3B).
   - Multivariate Cox regression (Supplementary Table 2) further verified that treatment modality was not an independent prognostic factor after adjusting for age, gender, race, diagnosis year, marital status, tumor size, histologic grade, and chemotherapy.



Supplementary Figure 1. Distribution of propensity scores.

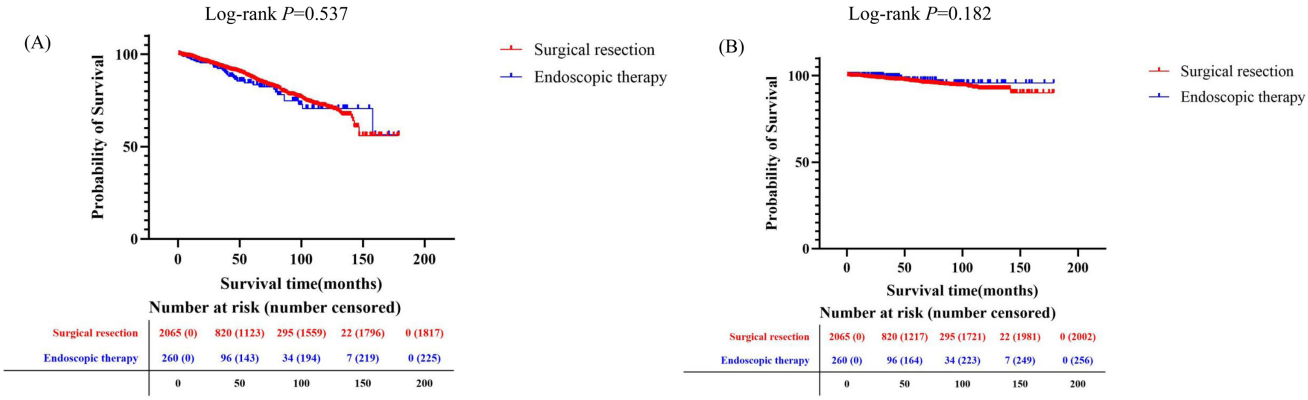
   - OS: endoscopic therapy vs. surgical resection, HR = 1.276 (95%CI: 0.889-1.832), *P* = .187.
   - CSS: endoscopic therapy vs. surgical resection, HR=0.856 (95%CI: 0.306-2.398), *P* = .767.
   - (1.2) **After PSM**



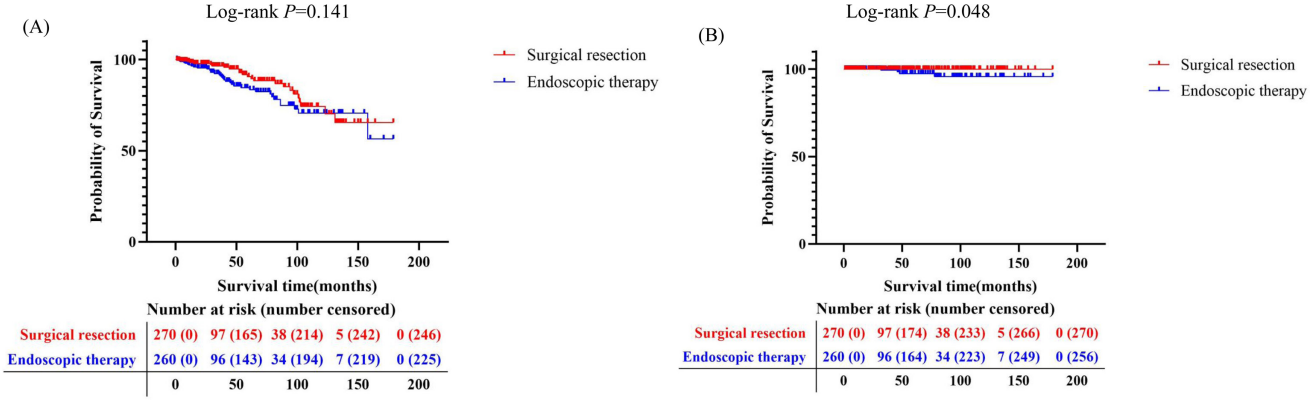
Supplementary Figure 2. Histogram of PSM.

Supplementary Table 1. Multivariate cox regression analysis of OS and CSS in patients after PSM

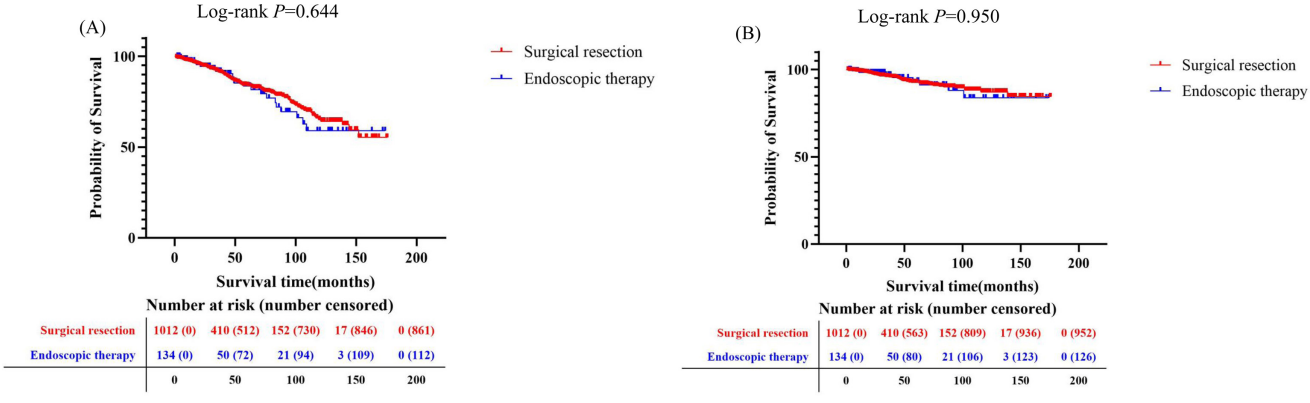
	OS		CSS	
Characteristics	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Therapeutic method				
Surgical resection	Reference		Reference	
Endoscopic therapy	1.344(0.901,2.007)	.148	2.193(0.739,6.502)	.157
Age, %				
<60	Reference		Reference	
≥60	3.162(1.811,5.522)	<.001	1.688(0.549,5.188)	.361
Gender, %				
Male	Reference		Reference	
Female	0.755(0.497,1.148)	.188	0.819(0.281,2.387)	.714
Race, %		.44		.273
White	Reference		Reference	
Black	1.369(0.777,2.412)	.277	2.800(0.753,10.415)	.125
Other	0.865(0.445,1.680)	.668	0.903(0.186,4.387)	.899
Year of diagnosis (%)		.128		.852
2007-2011	Reference		Reference	
2012-2016	1.119(0.678,1.845)	.661	0.710(0.216,2.330)	.572
2017-2021	0.587(0.291,1.184)	.137	0.820(0.186,3.619)	.793
Marital status (%)		.013		.243
Married	Reference		Reference	
Unmarried	1.933(1.246,2.998)	.003	2.531(0.851,7.526)	.095
Unknown	1.346(0.411,4.405)	.623	1.807(0.204,16.011)	.595
Tumor site, %				
Gastric	Reference		Reference	
Non-gastric	1.445(0.922,2.265)	.108	4.841(1.399,16.758)	.013
Tumor size, mm, %				
20-46mm	Reference		Reference	
47-100mm	1.218(0.793,1.872)	.367	2.134(0.721,6.316)	.171
Grade (differentiated), %		.108		.683
Well differentiated	Reference		Reference	
Moderately differentiated	1.009(0.618,1.647)	.97	1.525(0.391,5.949)	.544
Poorly differentiated	0.986(0.396.2.451)	.975	1.929(0.318,11.704)	.475
Undifferentiated	2.174(1.138,4.155)	.019	2.275(0.586,8.833)	.235
Chemotherapy, %				
Yes	Reference		Reference	
No	1.337(0.795,2.248)	.273	0.501 (0.157,1.596)	.242



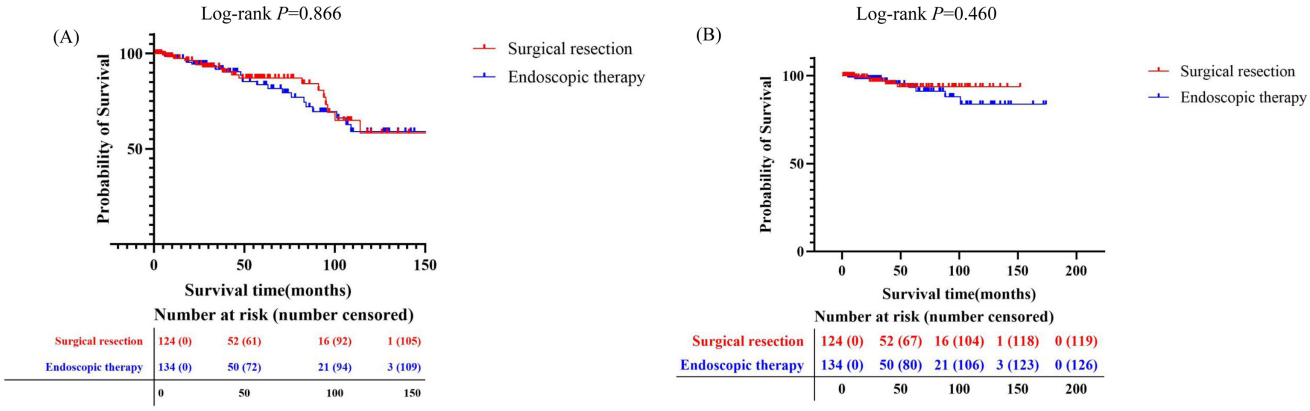
Supplementary Figure 3. Kaplan–Meier curves of overall survival and cancer-specific survival according to treatment methods before PSM in patients with gastric gastrointestinal stromal tumors (GISTs). (A) overall survival; (B) cancer-specific survival. Beyond 150 months, the number at risk was too small to yield reliable estimates.



Supplementary Figure 4. Kaplan–Meier curves of overall survival and cancer-specific survival according to treatment methods after PSM in patients with gastric gastrointestinal stromal tumors (GISTs). (A) overall survival; (B) cancer-specific survival. Beyond 150 months, the number at risk was too small to yield reliable estimates.



Supplementary Figure 5. Kaplan–Meier curves of overall survival and cancer-specific survival according to treatment methods before PSM in patients with non-gastric gastrointestinal stromal tumors (GISTs). (A) overall survival; (B) cancer-specific survival. Beyond 150 months, the number at risk was too small to yield reliable estimates.



Supplementary Figure 6. Kaplan–Meier curves of overall survival and cancer-specific survival according to treatment methods after PSM in patients with non-gastric gastrointestinal stromal tumors (GISTs). (A) overall survival; (B) cancer-specific survival. Beyond 150 months, the number at risk was too small to yield reliable estimates.

- For OS, the Log-rank test still showed no significant differences between the two treatments methods (P = .141, post-PSM Supplementary Figure 4A). For CSS, a borderline significant difference was observed (log-rank P = .048, post-PSM Supplementary Figure 4B), with slightly inferior CSS in the endoscopic therapy group.
- Notably, only 4 CSS events were captured in the post-PSM gastric GIST cohort, which was insufficient to construct a reliable multivariate Cox regression model. Thus, we only reported unadjusted Kaplan–Meier log-rank comparison for post-PSM CSS of gastric GISTs.

2. **Patients with non-gastric GISTs**
   - (2.1) **Before PSM**
   - Kaplan–Meier log-rank tests revealed no significant differences between surgical resection and endoscopic therapy for overall survival (OS, log-rank P = .644, Supplementary Figure 5A) or cancer-specific survival (CSS, log-rank P = .950, Supplementary Figure 5B).
   - Adjusted multivariate Cox regression (Supplementary Table 3) confirmed treatment exerted no independent prognostic influence.
   - OS: endoscopic therapy vs. surgical resection, HR=1.154 (95%CI: 0.731-1.824), P = .538.
   - CSS: endoscopic therapy vs. surgical resection, HR=1.066 (95%CI: 0.498-2.279), P = .869.
   - (2.2) **After PSM**
   - Log-rank tests demonstrated non-significant OS (P = .866, post-PSM Supplementary Figure 6A) and CSS (P = .460, post-PSM Supplementary Figure 6B) differences between endoscopic therapy and surgery. Multivariate Cox regression (Supplementary Table 4) consistently showed no independent survival difference associated with therapeutic approach.
   - OS: HR = 1.249 (95%CI: 0.639-2.442), P = .516.
   - CSS: HR = 1.785 (95%CI: 0.493–6.459), P = .377.

Supplementary Table 2. Multivariate Cox regression analysis of OS and CSS in patients with gastric gastrointestinal stromal tumors before PSM

	OS		CSS	
Characteristics	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Therapeutic method				
Surgical resection	Reference		Reference	
Endoscopic therapy	1.276(0.889,1.832)	.187	0.856(0.306,2.398)	.767
Age				
<60	Reference		Reference	
≥60	4.447(3.066,6.451)	<.001	2.472(1.352,4.519)	.003
Gender				
Male	Reference		Reference	
Female	0.611(0.479,0.780)	<.001	0.555(0.335,0.918)	.022
Race		.153		.626
White	Reference		Reference	
Black	1.147(0.871,1.510)	.33	1.307(0.757,2.256)	.337
Other	0.839(0.574,1.227)	.366	1.048(0.502,2.188)	.9
Year of diagnosis		.015		.003
2007-2011	Reference		Reference	
2012-2016	1.043(0.771,1.409)	.787	1.048(0.590,1.860)	.874
2017-2021	0.738(0.490,1.112)	.147	0.260(0.105,0.645)	.004
Marital status		.001		.531
Married	Reference		Reference	
Unmarried	1.624(1.263,2.089)	<.001	1.308(0.775,2.208)	.315
Unknown	1.052(0.593,1.867)	.863	0.811(0.246,2.669)	.73
Tumor size				
20-46mm	Reference		Reference	
47-100mm	1.342(1.052,1.713)	.018	1.714(1.007,2.916)	.047
Grade (differentiated)		.003		<.001
Well differentiated	Reference		Reference	
Moderately differentiated	0.976(0.728,1.308)	.871	1.673(0.839,3.336)	.144
Poorly differentiated	2.053(1.349.3.125)	0.001	5.537(2.576,11.901)	<.001
Undifferentiated	1.404(0.935,2.108)	.102	5.707(2.802,11.623)	<.001
Chemotherapy				
Yes	Reference		Reference	
No	1.136(0.850,1.519)	.389	0.685(0.403,1.163)	.161

Supplementary Table 3. Multivariate Cox regression analysis of OS and CSS in patients with non-gastric gastrointestinal stromal tumors before PSM

	OS		CSS	
Characteristics	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Therapeutic method				
Surgical resection	Reference		Reference	
Endoscopic therapy	1.154(0.731,1.824)	.538	1.066(0.498,2.279)	.869
Age				
<60	Reference		Reference	
≥60	2.855(1.975,4.126)	<.001	1.744(1.023,2.972)	.041
Gender				
Male	Reference		Reference	
Female	0.531(0.385,0.733)	<.001	0.318(0.182,0.556)	<.001
Race		.142		.472
White	Reference		Reference	
Black	1.301(0.785,2.157)	.308	1.354(0.599,3.063)	.467
Other	0.685(0.426,1.101)	.118	0.726(0.354,1.490)	.383
Year of diagnosis		.088		.027
2007-2011	Reference		Reference	
2012-2016	0.993(0.690,1.431)	.972	0.834(0.480,1.449)	.519
2017-2021	0.597(0.355,1.006)	.053	0.323(0.139,0.747)	.008
Marital status		.033		.222
Married	Reference		Reference	
Unmarried	1.536(1.107,2.131)	.01	1.584(0.934,2.687)	.088
Unknown	1.421(0.616,3.280)	.41	0.907(0.213,3.862)	.895
Tumor size				
20-46mm	Reference		Reference	
47-100mm	1.139(0.819,1.585)	.439	1.334(0.759,2.346)	.317
Grade (differentiated)		<.001		<.001
Well differentiated	Reference		Reference	
Moderately differentiated	1.656(1.125,2.437)	.01	2.637(1.333,5.217)	.005
Poorly differentiated	3.058(1.879.4.976)	<.001	5.128(2.317,11.350)	<.001
Undifferentiated	2.561(1.652,3.972)	<.001	5.043(2.481,10.249)	<.001
Chemotherapy				
Yes	Reference		Reference	
No	1.408(1.019,1.944)	.038	0.837(0.501,1.400)	.498

Supplementary Table 4. Multivariate Cox regression analysis of OS and CSS in patients with non-gastric gastrointestinal stromal tumors after PSM

	OS		CSS	
Characteristics	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Therapeutic method				
Surgical resection	Reference		Reference	
Endoscopic therapy	1.249(0.639,2.442)	.516	1.785(0.493,6.459)	0.377
Age				
<60	Reference		Reference	
≥60	2.673(1.142,6.258)	.023	2.194(0.502,9.578)	0.296
Gender				
Male	Reference		Reference	
Female	0.890(0.447,1.773)	.741	0.643(0.171,2.412)	.512
Race		.655		.185
White	Reference		Reference	
Black	1.756(0.524,5.882)	.361	4.652(0.881,24.560)	.07
Other	1.063(0.373,3.027)	.909	1.270(0.223,7.231)	.788
Year of diagnosis		.386		.72
2007-2011	Reference		Reference	
2012-2016	1.025(0.476,2.203)	.95	1.197(0.291,4.926)	.803
2017-2021	0.486(0.152,1.556)	.224	0.574(0.083,3.964)	.573
Marital status		.068		.135
Married	Reference		Reference	
Unmarried	2.104(0.988,4.478)	.054	3.060(0.837,11.188)	.091
Unknown	3.465(0.676,17.770)	.136	5.796(0.504,66.670)	.159
Tumor size				
20-46mm	Reference		Reference	
47-100mm	1.914(0.975,3.759)	.059	2.939(0.821,10.526)	.098
Grade (differentiated)		.641		.535
Well differentiated	Reference		Reference	
Moderately differentiated	1.488(0.673,3.292)	.326	2.721(0.547,13.538)	.221
Poorly differentiated	0.774(0.189.3.174)	.722	1.083(0.086,13.671)	.951
Undifferentiated	1.445(0.559,3.732)	.447	2.654(0.547,12.878)	.226
Chemotherapy				
Yes	Reference		Reference	
No	1.456(0.715,2.963)	.3	1.095(0.306,3.924)	.889