CANCER DIAGNOSIS & PROGNOSIS *5*: 668-676 (2025)
doi: 10.21873/cdp.10483

Impact of Surgical Refusal on Overall Survival in Patients With Rectal Cancer

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Abstract

Background/Aim: While surgery is a major component of treatment for managing rectal cancer, some individuals opt against it, potentially affecting their chances of survival. This study investigated the clinical and demographic elements linked to the decision to refuse surgery and assessed the potential impact of this decision on overall survival (OS).

Patients and Methods: We conducted a retrospective cohort study using the U.S. National Cancer Database to analyze factors linked to surgery refusal in patients with rectal cancer. Clinical, demographic and treatment characteristics were compared using Pearson chi-square and Wilcoxon rank-sum tests.

Results: Among the 115,066 patients with rectal cancer assessed for surgery, 2,675 individuals (2.3%) declined the procedure. Those who opted out were generally older, with a mean age of 71.9 years, exhibited a higher prevalence

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Received June 18, 2025 | Revised August 22, 2025 | Accepted September 5, 2025

of comorbid conditions, and were from racial minority groups or groups with lower socioeconomic status (p<0.001). OS analysis revealed that the cohort who refused surgery demonstrated a lower OS rate, with only 46% surviving for 5 years, in contrast to a 62% 5-year survival rate among those who underwent surgery.
Conclusion: Patients with rectal cancer may decline surgical treatment due to factors such as older age, frailty, and socioeconomic challenges. Addressing these obstacles may increase treatment acceptance and potentially lead to improved survival rates.

Keywords: Rectal cancer, cancer disparities, cancer survival, refusal, rectal cancer surgery.

Introduction

Cancer is the primary cause of death among individuals under 85 years of age. Colorectal cancer (CRC) ranks as the third most frequently diagnosed cancer and fourth leading cause of death related to cancer globally. In 2024, rectal cancer, a subset of CRC, accounted for 46,220 new cases out of a total of 152,810 CRC diagnoses (1). Rectal cancer predominantly affects older adults, with a significant increase in incidence observed between the ages of 40 and 50 years (2). Aging, along with environmental and genetic factors, plays a major role in the pathogenesis of CRC (3).

For individuals diagnosed with early-stage low-risk CRC, surgical resection may offer definitive treatment. Conversely, those with locally advanced rectal cancer, categorized as stage 2 (T3-4, N0) or stage 3 (any T, N+), gain additional advantages from a multidisciplinary combination of treatments, including chemotherapy, radiotherapy, or both. Patients found to have metastatic disease, contingent upon response to preoperative interventions and the cancer's pattern and spread, might still qualify for surgery (4). Considering that the elderly population is most frequently affected by rectal cancer and that surgical resection is a primary method for achieving a cure, it is essential to carefully evaluate treatment for patients with compromised functional status or existing comorbidities (3).

For individuals under 50 years, the survival rate at 1 year is 91.3%, while for those over 80, it is 75.5%. After 5 years, these rates are 87.0% for the under-50 age group and 57.1% for those over 80 (5). However, despite the well-documented advantages, certain patients decline surgical intervention, thereby posing unique challenges in clinical practice and potentially resulting in adverse health outcomes.

Reasons for declining surgery include concerns about potential side effects, a lack of adequate understanding of the procedure's advantages, and difficulties related to insurance and personal situations. Furthermore, racial and ethnic differences have been observed, with data indicating that Black and Asian/Pacific Islander individuals are more likely to refuse surgery compared to Whites (6, 7). Clear communication between healthcare professionals and patients is crucial. When communication is unclear, it can increase distrust, fear, and uncertainty, leading patients to refuse standard of care medical advice (8).

This study aimed to assess the impact of declining surgical intervention on OS of patients diagnosed specifically with rectal cancer, as well as to identify the demographic and clinical factors associated with such refusals. A comprehensive understanding of these disparities may facilitate the development of strategies to address patient concerns, reduce barriers to accessing care, and promote utilization of surgical treatments, thereby enhancing patient outcomes. By addressing the underlying reasons for surgery refusal, healthcare professionals may devise targeted interventions to increase acceptance and adherence to surgical recommendations, in the hopes of ultimately improving survival rates for patients with rectal cancer.

Patients and Methods

Design. This retrospective cohort study performed using data from the National Cancer Database (NCDB), spanning the years 2004 to 2019. The NCDB is a facility-based clinical surveillance registry established through a collaboration between the American Cancer Society and the American College of Surgeons' Commission on Cancer. It encompasses approximately 70% of new cancer cases in the United States, with data collected from over 1,500 accredited facilities (9). Institutional Review Board approval was not required for this study, as the NCDB data is de-identified.

Study population. The NCDB was utilized to identify patients diagnosed with rectal cancer. The sociodemographic variables considered included age at diagnosis, race, ethnicity, sex, income, and insurance status (9, 10). Income was defined as the median household income for each patient's zip code, based on data from the American Community Survey and adjusted for inflation. The classification of treatment facility type adhered to the Commission on Cancer's categorization based on program structure, services provided, and caseload (11). The rural, urban, or metropolitan classification was determined using rural-urban continuum codes from the United States Department of Agriculture Economic Research Service, based on each patient's county (12). Clinical characteristics included treatment type, stage, and grade, with staging following the guidelines of the American Joint Committee on Cancer's sixth and seventh editions (13). Health insurance type was defined as private, government (Medicare and Medicaid), uninsured, and unknown.

Statistical analysis. Descriptive statistics were employed to summarize the sociodemographic and clinical characteristics of the patients. Associations between categorical variables and the refusal of surgery were examined using Pearson's chi-square tests, with results presented as frequencies and relative frequencies. For continuous variables, the Wilcoxon rank-sum test was utilized, with data presented as medians, means, and standard deviations. OS was defined as the duration from cancer diagnosis to death. Factors associated with OS were analyzed using both univariable and multivariable Cox proportional hazards models. OS was further analyzed using the Kaplan–Meier method, with survival curves compared *via* the log-rank test. Statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient characteristics. The study encompassed 115,066 patients diagnosed with rectal cancer, as identified in the NCDB for 2024. The demographic characteristics of these patients are detailed in Table I. The mean age of the cohort was 63.2 years, and 61.2% of the patients were male. Regarding racial composition, 85.6% were White, 8.6% Black, 3.6% Asian, and 0.5% Native American. Notably, 81.4% (92,979) of the patients underwent surgical intervention, whereas only 2.3% (2,675) actually declined surgery. Patients who refused surgery had a higher mean age of 71.9 years compared to the overall mean of 63.2 years ($p<0.001$).

Factors associated with surgery refusal. Our analysis indicated that the refusal of surgical intervention was more prevalent among older patients with those declining surgery having a mean age of 71.9 years, which was significantly higher than that of patients who consented to surgery. Racial disparities were evident, as Black and Asian patients represented higher proportions among those refusing surgery (13% and 14.7%, respectively, compared to 8.6% and 3.6% in the overall cohort, $p<0.001$). Socioeconomic and geographic factors were also influential; individuals with lower income levels and those residing in rural areas demonstrated a higher likelihood of refusing surgery. Additionally, a lack of insurance coverage was associated with increased refusal rates, with uninsured patients comprising 4.4% of the refusals. Clinical factors contributing to surgery refusal included

Table I. *Baseline characteristics of patients with rectal cancer stratified by surgery status and reason for not undergoing surgery.*

Variable	Overall	Had surgery	Reason for not undergoing surgery				*p*-Value
			Not part of treatment plan	Co-morbidities	Unknown	Patient refused	
Total, n (%)	115,066 (100)	92,979 (81.4)	13,220 (11.6)	2,361 (2.1)	3,010 (2.6)	2,675 (2.3)	
Age, years							
Mean±SE	63.2±0.0	62.0±0.0	67.7±0.1	74.4±0.3	62.8±0.2	71.9±0.3	**<0.001**
Sex, n (%)							
Male	70,382 (61.2)	56,918 (61.2)	7,978 (60.3)	1,388 (58.6)	1.978 (65.7)	1,627 (60.8)	**<0.001**
Female	44,684 (38.8)	36,061 (38.8)	5,242 (39.7)	979 (41.4)	1,032 (34.3)	1,048 (39.2)	
Race, n (%)							
White	98,506 (85.6)	80,413 (86.5)	10,848 (82.1)	2,018 (85.3)	2,428 (80.7)	2,137 (79.9)	**<0.001**
Black	9,878 (8.6)	7,285 (7.8)	1,540 (11.6)	247 (10.4)	365 (12.1)	348 (13.0)	
Native American	536 (0.5)	432 (0.5)	62 (0.5)	7 (0.3)	16 (0.5)	17 (0.6)	
Asian	4,195 (3.6)	3,396 (3.7)	462 (3.5)	71 (3)	117 (3.9)	125 (4.7)	
Other	1,951 (1.7)	1,453 (1.6)	308 (2.3)	24 (1)	84 (2.8)	48 (1.8)	
Ethnicity, n (%)							
Non-Hispanic	102,900 (93.9)	83,433 (94.2)	11,666 (92.3)	2,165 (95.9)	2,507 (88.9)	2,427 (94.9)	**<0.001**
Hispanic	6,704 (6.1)	5,146 (5.8)	967 (7.7)	92 (4.1)	313 (11.1)	131 (5.1)	
Health insurance type							
Uninsured	4,483 (3.9)	3,389 (3.6)	694 (5.2)	80 (3.4)	177 (5.9)	119 (4.4)	**<0.001**
Private	50,416 (43.8)	44,051 (47.4)	4,061 (30.7)	368 (15.5)	1,135 (37.7)	604 (22.6)	
Government	57,860 (50.3)	43,886 (47.2)	8,203 (62.0)	1,889 (79.8)	1,607 (53.4)	1,913 (71.5)	
Unknown	2,307 (2.0)	1,653 (1.8)	262 (2.0)	30 (1.3)	91 (3.0)	39 (1.5)	
Median household income, n (%)							
<$63,000	72,861 (69.0)	58,222 (68.6)	8,904 (71.3)	1,596 (72.0)	1,891 (68.5)	1,733 (70.4)	**<0.001**
≥$63,000	32,670 (31.0)	26,608 (31.4)	3,580 (28.7)	622 (28.0)	869 (31.5)	727 (29.6)	
Treatment area, n (%)							
Metropolitan	79,515 (71.4)	63,800 (71.0)	9,463 (73.7)	1,650 (71.6)	2,139 (73.1)	1,902 (73.0)	**<0.001**
Urban	26,012 (23.4)	21,261 (23.6)	2,818 (21.9)	531 (23.0)	653 (22.3)	584 (22.4)	
Rural	5,821 (5.2)	4,844 (5.4)	564 (4.4)	123 (5.3)	136 (4.6)	118 (4.5)	
Clinical stage, n (%)							
0	1,247 (1.1)	1,047 (1.1)	139 (1.1)	16 (0.7)	15 (0.5)	20 (0.7)	**<0.001**
I	25,963 (22.6)	21,855 (23.5)	2,633 (19.9)	417 (17.6)	419 (13.9)	462 (17.3)	
II	41,552 (36.1)	32,690 (35.2)	5,208 (39.4)	1,068 (45.1)	1,221 (40.6)	1,088 (40.7)	
III	46,304 (40.2)	37,387 (40.2)	5,240 (39.6)	866 (36.6)	1,355 (45.0)	1,105 (41.3)	
Chemotherapy, n (%)							
No	25,522 (22.5)	19,261 (21.0)	3,888 (30.2)	892 (38.3)	369 (13.2)	892 (33.5)	**<0.001**
Yes	87,758 (77.5)	72,654 (79.0)	8,982 (69.8)	1,440 (61.7)	2,422 (86.8)	1,770 (66.5)	
Chemotherapy sequence, n (%)							
No chemotherapy	37,304 (36.0)	17,678 (21.1)	11,979 (99.1)	2,140 (98.9)	2,572 (99.5)	2,497 (99.8)	**<0.001**
Neoadjuvant	37,759 (36.4)	37,704 (44.9)	36 (0.3)	12 (0.6)	3 (0.1)	2 (0.1)	
Adjuvant	9,648 (9.3)	9,562 (11.4)	64 (0.5)	8 (0.4)	10 (0.4)	3 (0.1)	
Peri-operative	18,976 (18.3)	18,963 (22.6)	10 (0.1)	3 (0.1)			
Facility type, n (%)							
Community	10,728 (9.7)	7,954 (8.9)	1,698 (13.2)	301 (12.8)	395 (13.8)	294 (11.1)	**<0.001**
Comprehensive	45,831 (41.3)	37,219 (41.6)	5,098 (39.6)	1,026 (43.7)	1,090 (38.0)	1,128 (42.7)	
Academic/Research	39,160 (35.3)	31,623 (35.3)	4,594 (35.7)	697 (29.7)	1,039 (36.3)	847 (32.0)	
Integrated network	15,259 (13.7)	12,681 (14.2)	1,470 (11.4)	325 (13.8)	342 (11.9)	374 (14.2)	
Operation type, n (%)							
No surgery	30,093 (26.2)	8,332 (9.0)	13,214 (100)	2,367 (100)	2,938 (100)	2,674 (100)	**<0.001**
Partial colectomy	58,902 (51.3)	58,902 (63.3)					
Total or near total colectomy	22,876 (19.9)	22,876 (24.6)					
Surgery NOS	2,869 (2.5)	2,869 (3.1)					

Table I. *Continued*

Table I. *Continued*

Variable	Overall	Had surgery	Reason for not undergoing surgery				*p*-Value
			Not part of treatment plan	Co-morbidities	Unknown	Patient refused	
Tumor grade, n (%)							
I	9,074 (9.3)	7,485 (9.2)	983 (10.1)	142 (8.2)	236 (10.6)	173 (8.7)	**<0.001**
II	77,202 (78.9)	64,441 (79.0)	7,491 (77.3)	1,374 (79.3)	1,764 (79.2)	1,633 (82.2)	
III	10,666 (10.9)	8,826 (10.8)	1,180 (12.2)	202 (11.7)	215 (9.6)	177 (8.9)	
IV	882 (0.9)	811 (1.0)	40 (0.4)	14 (0.8)	13 (0.6)	3 (0.2)	

NOS: Not otherwise specified; SE: standard error. Associations between columns were assessed using the Wilcoxon rank-sum test for ordinal responses and the Pearson chi-square test for categorical responses. Statistically significant *p*-values are shown in bold.

the presence of severe comorbidities, which influenced the decision against surgery in frail patients.

Overall survival. The analysis of OS also revealed differences in outcome based on surgical intervention (Table II). The 1- and 5-year OS rates for the whole cohort of patients were 91% and 61%, respectively. Patients who underwent surgery had a 5-year survival rate of 62%, with a median survival of 74.5 months. In contrast, those who declined surgery demonstrated a lower 5-year survival rate of 46% and a median survival of 56.6 months. The log-rank test confirmed statistically significant differences in OS between the surgical and non-surgical groups ($p<0.001$), as illustrated in Figure 1 and Table III.

Discussion

This study investigated the impact of refusing surgical intervention on OS in patients diagnosed with rectal cancer, as well as the demographic and clinical characteristics associated with such refusals. The results demonstrated that patients who declined surgery exhibited significantly lower OS rates at both 1- and 5-year intervals compared to those who underwent surgical treatment. Factors associated with the decision to refuse surgery included advanced age, male sex, specific racial and ethnic backgrounds, a lower income level, and either lack of insurance or reliance on public insurance programs.

Individuals who declined surgical intervention were notably older. These results align with earlier research indicating that older adults are more likely to refuse treatment (12, 14). Research has indicated that patient concerns about potential risks or side-effects play a crucial role in older adults' decisions to decline cancer treatment (6, 12). This is especially important because older individuals face a greater likelihood of encountering complications from rectal surgery than younger patients (15). Addressing these concerns by improving communication and offering thorough pre-surgical counselling might result in greater acceptance of surgery and enhanced outcomes for this group.

More men than women opted out of surgery, a pattern that aligns with observations in other cancer types such as melanoma and lung cancer. This potentially reflects a broader healthcare trend where men are generally less inclined to seek medical treatment compared to women (8, 16). Additionally, significant racial differences were observed, with Black and Asian patients showing higher rates of declining surgery. This is consistent with research on other cancer types, reflecting complex obstacles related to cultural, socioeconomic, and systemic issues (12, 17). Previous research suggests that shared decision-making, supported by decisional aids, can greatly benefit patients from racial and ethnic minority groups by enhancing their medical understanding and increasing the chances of them opting for surgery (17, 18).

Economic considerations were significantly associated with the decision to decline surgery, with individuals from

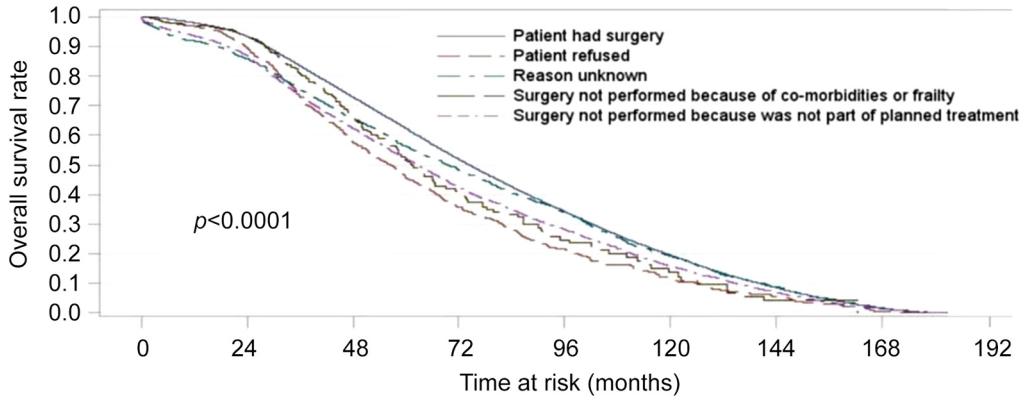
Table II. *Cox proportional hazards model for overall survival of patients with rectal cancer.*

Variable	Variable	Univariable analysis		Multivariable analysis	
		HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	Per 10-year increase	1.00 (1.00-1.00)	**<0.001**	1.00 (0.99-1.00)	**<0.001**
Chemotherapy sequence	Adjuvant	0.84 (0.81-0.86)	**<0.001**	0.91 (0.88-0.95)	**<0.001**
	Neoadjuvant	0.90 (0.87-0.92)	**<0.001**	0.97 (0.94-0.99)	**0.013**
	Peri-operative	1.10 (1.07-1.13)	**<0.001**	1.18 (1.15-1.22)	**<0.001**
	No chemotherapy	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Facility type	Academic or research	1.05 (1.01-1.09)	**0.006**	1.04 (1.00-1.08)	**0.038**
	Comprehensive cancer	0.96 (0.93-1.00)	**0.028**	0.97 (0.94-1.00)	0.081
	Integrated network	0.99 (0.95-1.04)	0.746	1.00 (0.96-1.04)	0.938
	Community cancer	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Tumor grade	I	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
	II	0.97 (0.94-1.00)	0.092	0.97 (0.94-1.00)	**0.040**
	III	0.84 (0.80-0.88)	**<0.001**	0.84 (0.80-0.88)	**<0.001**
	IV	1.11 (0.99-1.23)	0.074	1.13 (1.01-1.26)	**0.031**
Ethnicity	Hispanic	1.22 (1.18-1.27)	**<0.001**	1.20 (1.15-1.25)	**<0.001**
	Non-Hispanic	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
	>$63,000	1.04 (1.01-1.06)	**<0.001**	1.04 (1.02-1.06)	**<0.001**
	<$63,000	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Health insurance type	Uninsured	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
	Private	0.94 (0.90-0.99)	**0.015**	0.99 (0.94-1.04)	0.699
	Non-private	0.93 (0.88-0.97)	**0.002**	1.04 (0.98-1.09)	0.173
	Unknown	1.00 (0.91-1.08)	0.925	1.04 (0.96-1.14)	0.327
Race	Asian or Pacific Islander	1.18 (1.12-1.23)	**<0.001**	1.16 (1.11-1.22)	**<0.001**
	Black	1.05 (1.02-1.09)	**0.004**	1.04 (1.01-1.08)	0.025
	Native American	1.23 (1.07-1.41)	**0.004**	1.19 (1.04-1.37)	0.014
	Other	1.34 (1.23-1.46)	**<0.001**	1.23 (1.13-1.34)	**<0.001**
	White	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Surgical status and reason	Patient refused surgery	1.53 (1.41-1.66)	**<0.001**	1.56 (1.43-1.70)	**<0.001**
	Reason for no surgery unknown	1.22 (1.14-1.31)	**<0.001**	1.22 (1.14-1.32)	**<0.001**
	Surgery was not performed because of comorbidities	1.11 (0.94-1.32)	0.219	1.16 (0.97-1.37)	0.096
	Surgery was not part of planned treatment	1.30 (1.25-1.35)	**<0.001**	1.30 (1.25-1.36)	**<0.001**
	Patient had surgery	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Sex	Male	1.01 (0.99-1.03)	0.329	0.99 (0.98-1.01)	0.601
	Female	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]

These statistics describe the association between the covariable of interest and the survival time. No other covariables were included in the model. The sample had 42,638 events, 24,656 censored, and 67,294 total. Statistically significant *p*-values are shown in bold.

lower-income brackets and those lacking private insurance being more likely to refuse surgical procedures. Patients with lower incomes and no insurance are more likely to decline surgical procedures. The cost of paying out-of-pocket can be a major obstacle to obtaining surgical care for those who are uninsured and have limited financial means (19). Programs designed to assist patients in navigating the healthcare system and overcoming challenges in accessing cancer care have been demonstrated to increase the likelihood of patients receiving the recommended cancer treatments (18).

Similarly to our study, a retrospective cohort analysis conducted from 2004 to 2015 using the NCDB (which included 55,704 patients diagnosed with rectal cancer) (20) showed that 2.6% declined surgical intervention. The 5-year OS for patients who had surgery was 61.6% in that study, which is very similar to what we found (61%), but 5-year OS for patients who refused surgery was 35.7%, which is lower than what we found (46%). However, our study included a larger cohort and a more recent dataset, providing a more robust and comprehensive analysis of



	Number at risk								
Time (months)	0	24	48	72	96	120	144	168	180
Patient had surgery	92,979	79,520	56,508	37,795	25,014	16,249	10,779	7,303	4,513
Patient refused	13,220	7,585	4,586	3,183	2,391	1,883	1,580	1,380	824
Reason unknown	2,361	1,309	893	800	756	514	448	302	75
Surgery not performed (comorbidities)	3,010	2,200	1,677	1,258	1,017	689	564	472	148
Surgery not performed (not part of treatment)	2,675	1,722	903	683	552	491	460	325	107

Figure 1. *Kaplan–Meier analysis of overall survival of patients with rectal cancer according to performance or not of surgery. Survival curves were compared via the log-rank test.*

Table III. *Overall survival rates stratified by surgery status and reason for refusal of surgery.*

	Survival rate, n (%)		
	1 Year (95% CI)	5 Years (95% CI)	Median (95% CI), months
Total	0.97 (0.97-0.97)	0.61 (0.61-0.61)	73.0 (72.6-73.5)
Patient had surgery	0.98 (0.98-0.98)	0.62 (0.62-0.63)	74.5 (74.0-74.9)
Surgery not performed because it was not part of treatment plan	0.94 (0.93-0.94)	0.52 (0.51-0.53)	62.8 (61.2-64.4)
Surgery not performed because of comorbidities	0.97 (0.96-0.93)	0.52 (0.45-0.58)	61.4 (57.7-66.8)
Reason unknown	0.92 (0.91-0.93)	0.56 (0.54-0.59)	69.6 (65.9-72.4)
Patient refused	0.97 (0.96-0.97)	0.46 (0.43-0.49)	56.6 (53.2-59.4)

CI: Confidence interval. All differences were significant at $p<0.001$.

this trend. While the reasons for refusal remained consistent, it is essential to validate our collective findings in a prospective cohort and with more recent data. Nonetheless, our study contributes to the existing body of knowledge.

The association between the refusal of surgery and reduced survival rates highlights the essential role of surgical procedures in the management of rectal cancer. The reduced OS rates among individuals who forgo surgery emphasize the urgent necessity to understand and address the factors contributing to surgical hesitancy. Initiatives aimed at educating patients about the survival benefits of surgical treatments, coupled with robust support systems, are critical for increasing treatment acceptance and improving patient outcomes.

We recognize the presence of significant limitations in our study. The NCDB lacks data on the cause of death, recurrence, and more specific reasons for declining surgery, which prevents a more comprehensive analysis of these aspects. Furthermore, the database does not account for factors such as cultural and religious influences that may influence the decision to refuse surgery. The retrospective nature of this study may also have affected its ability to accurately reflect current

treatment practices, such as the growing trend towards non-operative therapy for rectal cancer following complete response to neoadjuvant therapy.

Conclusion

The study demonstrated that individuals diagnosed with rectal cancer who declined the recommended surgical intervention exhibited lower OS rates compared to those who underwent surgery. These findings highlight significant disparities in the refusal of surgical treatment, reflecting the need to ensure equitable access to surgical care. Addressing disparities is essential for improving survival rates among all patients in the treatment of rectal cancer.

Conflicts of Interest

The Authors declare no conflicts of interest in relation to this study.

Authors' Contributions

Vishal Abhimutt Mahesh was responsible for writing the original draft. Vishal Abhimutt Mahesh and Emmanuel Gabriel were responsible for conceptualization, methodology, investigation, and visualization. Emmanuel Gabriel was responsible for validation, formal analysis, resources, data curation, supervision, and funding acquisition. Vishal Abhimutt Mahesh, Anjali Yadav, Harsheen Kaur Manaise, Berkay Demirors, Paola Berrios Jiminez, Angel Aguayo-Merly, Jade C. Bowers, Bansi P. Savaliya, Reed Popp, Ramin Shekouhi, Guido Chiriboga, Syeda Hoorulain Ahmed, Fatima Mubarak, EsinamEkpeh and Emmanuel Gabriel were responsible for reviewing and editing.

Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine-learning software, were used in the preparation, analysis, or presentation of this manuscript.

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