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Rectal Cancer Patients Younger Than 50 Years Lack a Survival Benefit From NCCN Guideline–Directed Treatment for Stage II and III Disease

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Abstract

BACKGROUND: The incidence of rectal cancer in patients younger than 50 years is increasing. To test the hypothesis that the biology in this younger cohort may differ, this study compared survival patterns, stratifying patients according to National Comprehensive Cancer Network (NCCN) guideline–driven care and age.

METHODS: The National Cancer Data Base was queried for patients treated with curative-intent transabdominal resections with negative surgical margins for stage I to III rectal cancer between

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AUTHOR CONTRIBUTIONS

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Additional supporting information may be found in the online version of this article.

CONFLICT OF INTEREST DISCLOSURES

Thomas J. George reports acting as a consultant for Merck and Bayer for work performed outside of the current study. His institutional research has been supported by Incyte, Bristol-Myers Squibb, Bayer, Merck, NewLink, AstraZeneca/Med-Immune, and Tesaro.

2004 and 2014. Outcomes and overall survival for patients younger than 50 years and patients 50 years old or older were compared by subgroups based on NCCN guideline–driven care.

RESULTS: A total of 43,106 patients were analyzed. Younger patients were more likely to be female and minorities, to be diagnosed at a higher stage, and to have travelled further to be treated at academic/integrated centers. Short- and long-term outcomes were significantly better for patients younger than 50 years, with age-specific survival rates calculated. Younger patients were more likely to receive radiation treatment outside NCCN guidelines for stage I disease. In younger patients, the administration of neoadjuvant chemoradiation for stage II and III disease was not associated with an overall survival benefit.

CONCLUSIONS: Age-specific survival data for patients with rectal cancer treated with curative intent do not support an overall survival benefit from NCCN guideline–driven therapy for stage II and III patients younger than 50 years. These data suggest that early-onset disease may differ biologically and in its response to multimodality therapy.

Keywords

National Cancer Data Base (NCDB); rectal cancer; survival; treatment appropriateness

INTRODUCTION

Colorectal cancer is the third most common cancer and second leading cause of cancer death in the United States. Although the overall incidence of rectal cancer is decreasing in patients older than 50 years,[1] likely because of improved screening adherence,[2] there has been a disproportionate increase in rectal cancer incidence in patients younger than 50 years.[3,4] Furthermore, overall mortality for colorectal cancer is improving, but not for these younger patients; their mortality rate from rectal cancer over time has increased from 1970 to 2014.[5,6] On the basis of single-institution studies, this is thought to primarily be a result of delays in diagnosis in the younger cohort.[7] The notion that these early-onset cases represent differences in epidemiology and perhaps responses to therapy is emerging.

National Comprehensive Cancer Network (NCCN) guidelines define the current standard of care for the intended cure of rectal cancer as surgical resection alone for stage I disease[8] and as neoadjuvant chemoradiation therapy with subsequent surgical resection and systemic chemotherapy for stage II and III disease.[8,9] However, these recommendations and current survival estimates are predominantly influenced by trials or databases with patients older than 50 years, with younger patients not well studied. To address this gap in our knowledge and to test the hypothesis that the biology in patients younger than 50 years may differ, we aimed to analyze survival patterns in the younger cohort. This work queried a large national database for patients with rectal cancer who underwent curative-intent treatment to compare outcomes in cohorts defined by adherence to NCCN guidelines and age.

MATERIALS AND METHODS

A retrospective review of the National Cancer Data Base (NCDB) was performed after approval by the institutional review committee. Briefly, the NCDB is a hospital-based, national registry of de-identified cancer patients and a joint project of the Commission

on Cancer of the American College of Surgeons and the American Cancer Society. The participant user file analyzed in this study included all patients diagnosed with rectal cancer from 2004 through 2014. Inclusion criteria consisted of histologically proven rectal adenocarcinoma in patients undergoing curative-intent surgical resection for stage I to III disease. Patients with carcinoma in situ and metastatic disease were excluded. Patients undergoing local excision and those with positive surgical margins were also excluded to control for the type and quality of surgical resection because no variable for the quality of total mesorectal excision was available in the NCDB. Patients receiving adjuvant radiation were excluded because this was uncommon, patients were equally distributed across age groups, and reasons for adjuvant radiation were undocumented. Patients at the extremes of age (<20 and >75 years) and those who did not receive chemotherapy because of comorbidities or death were excluded to control for age-based survival differences. Finally, patients with pertinent, missing variables were excluded. A detailed inclusion diagram is shown in Figure 1. Patients were cohorted by adherence to NCCN-based guidelines (as defined previously) for treatment and by age (< or ≥50 years).

The statistical analysis was conducted with IBM SPSS Statistics (version 23). Variables were analyzed with the exact chi-square test and the independent sample *t* test for categorical and continuous variables, respectively. Survival curves were estimated with Kaplan-Meier methodology, and differences between groups were assigned with logrank, Breslow, and Tarone-Ware tests. Time-specific mortality rates for 3-, 5-, 7-, and 10-year mortality were calculated with life tables. Relative survival was calculated with expected survival values obtained from a time- and age-matched cohort in the Surveillance, Epidemiology, and End Results database.[10] Survival curves were re-estimated for the younger (<50 years) and older cohorts (≥50 years) and were substratified by patients who did or did not receive NCCN guideline–driven care. Variables that were significant in a univariate analysis for overall survival were included in a multivariate Cox proportional hazards regression model. The univariate and multivariate analyses were repeated for the age-based cohorts. A *P* value <.05 was considered statistically significant. All analysis involving neoadjuvant therapy groups was repeated for clinical and pathologic stages to confirm the absence of a statistical difference in the results. Clinical and pathologic TNM staging was performed according to American Joint Committee on Cancer guidelines, with 54% and 46% of the patients classified according to the sixth and seventh editions, respectively.[8]

RESULTS

Patient Population Overall

Of the 243,666 patients with rectal cancer over the 10-year period in the NCDB, 43,106 patients were included in the final analysis. Only 9126 patients (21%) were younger than 50 years. Baseline demographic and clinical data stratified by age are presented in Table 1. The younger cohort had a significantly higher proportion of females and minorities (African Americans, Hispanics, and Asians), was more likely to be uninsured, and had fewer comorbid conditions. The younger patients were more likely to reside in a metropolitan area, earn a higher income, travel further for medical care, and be treated at integrated and/or

academic cancer centers. Oncologically, the younger patients were significantly more likely to be diagnosed at a higher pathologic stage (stage III, 40% vs 31%; $P<.001$) and were more likely to have poorly differentiated lesions and mucinous or signet ring cell lesions. No significant difference was noted in the clinicodemographic information within the younger population, even when deciles were being compared.

Patient Population by Age

We sought to evaluate differences in the accuracy of clinical staging (stage I) and the degree of downstaging noted with neoadjuvant therapy (stages II and III) across age cohorts. The concordance of clinical and pathologic stages stratified by age revealed no difference across age groups, and this suggested equal accuracy of clinical staging (Fig. 2). For internal validity, a high concordance (95%) was noted in patients with clinical and pathologic stage I disease who did not receive radiation or chemotherapy. In terms of treatment, younger patients were more likely to receive radiation therapy for all stages. This was applicable to stage I disease (radiation therapy, 41.9% for young patients vs 31.7% for old patients; $P<.001$) and stage II and III disease (chemoradiation therapy, 93.6% vs 88.1%; $P<.001$). Thus, fewer patients in the younger cohort received NCCN guideline–directed therapy for stage I disease, but a greater percentage received it for stage II and III disease.

Postoperative Outcomes by Age

Younger patients experienced shorter hospital stays (6.7 vs 8.0 days; $P<.001$), but 30-day readmission rates were similar between groups. The younger cohort had better short-term mortality and long-term survival rates than their older counterparts. Both the 30-day mortality rate (2.0% vs 0.2%; $P<.001$) and the 90-day mortality rate (3.7% vs 0.5%; $P<.001$) were higher in the older cohort. This difference became more pronounced with 3-, 5-, and 10-year survival rates, as shown in Figure 3A, and it persisted independently for stage I, II, and III disease (Fig. 3B–D). The Kaplan-Meier analysis revealed a significant survival advantage for younger patients at 12 years (9.8 vs 8.7 years; $P<.001$). No significant survival difference was noted within the younger population by deciles (Fig. 3).

A univariate and multivariate analysis of overall survival for the entire group was performed to investigate the impact of individual factors on patients' survival, and this demonstrated relations with known clinicopathologic factors. The analysis revealed a hazard ratio of 2.2 for patients who were 50 years of age or older (confidence interval, 2.0–2.2; $P<0.01$). Factors associated with poorer overall survival were male sex, African American race, a higher comorbidity index, nonprivate insurance, a lower income level, treatment at community hospitals (vs academic centers or integrated networks), a higher pathologic stage, a poorly differentiated/undifferentiated tumor, and a mucinous or signet ring cell histology.

To determine the contributory role of age to overall survival in the context of other demographic and pathologic factors, a Cox regression multivariate analysis was performed for both age cohorts (Table 2). The aforementioned factors associated with survival for the study population maintained significance across age cohorts, except for the following differences: For patients younger than 50 years, the survival benefits of being Asian and

Hispanic and being treated at academic/integrated networks and the survival detriments of African American race, being uninsured, and an increasing numeric age disappeared.

Survival by NCCN Guideline–Driven Care and Age

To determine the impact of age and stage-appropriate NCCN guideline–driven care on survival, the Kaplan-Meier analysis was stratified by these 2 variables (Supporting Figs. 1 and 2). In the older group, survival improved with the receipt of NCCN guideline–driven care for stage II and III disease (Figs. 4A and 5A). The 14% survival benefit for the older patients with stage II and III disease receiving stage-appropriate therapy at 5 years persisted over the long term (11% survival benefit in 10-year overall survival). In contrast, although the younger population showed a survival benefit from NCCN guideline–driven care for stage I disease (Fig. 4B), it failed to show a survival benefit when NCCN guidelines were followed for stage II and III disease (Fig. 5B). Treatment details for the patients in the outside-NCCN group are shown in Figures 4 and 5; the majority of clinical stage I patients in that group received neoadjuvant chemoradiation therapy (80%), whereas the majority of clinical stage II and III patients in that group failed to receive neoadjuvant radiation therapy (85%). A separate subgroup analysis for stage II and III disease patients was performed. Further age substratification revealed that following NCCN-guideline–driven care led to significantly reduced survival in patients younger than 45 years ($P<.03$), no actuarial survival benefit until an age ≥50 years, and a statistically significant survival benefit only at an age>54 years (Supporting Fig. 3). A Cox regression multivariate analysis stratified by both age cohorts (Table 2), when limited to patients with stage II and III disease, confirmed a lack of a survival benefit for the younger cohort when NCCN guideline–driven care was followed.

DISCUSSION

Survival data specific to younger patients with rectal cancer are lacking in the literature. Furthermore, current recommendations for therapy are based on results from trials that predominantly accrued patients of older ages. Using a large, national database to evaluate more than 43,000 patients with rectal cancer over a 10-year time period, our study provides data showing that early-onset rectal cancer may differ in its epidemiology, biology, and response to current treatment regimens. Specifically, our analysis suggests that survival advantages associated with stage-appropriate NCCN guideline–driven care for stage II and III disease do not appear to be realized in patients younger than 50 years. We also provide age-specific survival data for the younger group in the largest cohort studied to date.

Our data suggest that patients younger than 50 years with rectal cancer differ at presentation in comparison with the more aged cohort. They are more likely to be female, minorities, and uninsured. They are more likely to be diagnosed at a higher stage and have poor tumor differentiation and other histological features associated with worse outcomes (mucinous or signet ring cell histology). In contrast, they are more likely to travel further to receive medical treatment and are more likely to receive treatment at academic centers/integrated treatment centers. They have better overall survival in comparison with the cohort 50 years of age and older.

Younger patients appear to have better short-term (shorter hospital stays and better 30- and 90-day mortality) and long-term outcomes (higher 3-, 5-, 7-, and 10-year survival rates). Although survival was previously known to be better in young patients, our study shows no difference in survival by deciles up to the age of 50 years, after which the prognosis worsens by each decile. This held true in the multivariate analysis. This is an interesting finding because the younger group fares better over the long term despite a higher incidence of several factors associated with poor outcomes in the multivariate analysis for the entire group, such as African American race, an uninsured/Medicaid status, a higher pathologic stage, a poorly differentiated/undifferentiated tumor, and a mucinous/signet ring cell histology.

Because enrollment in prior randomized controlled trials has been limited to patients older than 50 years, this age group primarily drives outcome data. Our study is the largest to report current long-term survival data for the younger population for prognostic and research purposes. In addition, not only is there a difference in the prevalence of stage-appropriate NCCN guideline–driven care for the younger group, younger patients also appear to respond differently to such treatment. For stage II and III disease, younger patients are more likely to receive NCCN guideline–driven care (chemoradiation and surgical resection), but this does not seem to affect their survival. In contrast, older patients show a large and significant survival benefit from it. A higher incidence of microsatellite instability, which has been demonstrated in younger patients with colon cancer,[11] could explain the reduced effectiveness of conventional adjuvant therapy in our study. However, genetic data are not available in the NCDB, and the exclusion of more proximal colonic tumors in our study, which are more likely microsatellite instability–high,[12] makes conclusions difficult to achieve.

A treatment-selection bias in favor of aggressive treatment for the younger cohort, in turn affecting survival rates, cannot be excluded, but that would lead to the opposite results (ie, a bigger survival benefit for the younger cohort). Previous studies have shown patients older than 75 years to be less likely to receive optimal NCCN guideline–driven care.[13,14] We attempted to control for this by requiring all patients to have undergone transabdominal resection with negative margins to emulate treatment with an intent to cure and by excluding patients older than 75 years from the analysis. Regardless, the study findings, including the fact that NCCN guideline–driven care did not affect survival in the younger population with stage II and III disease, were similar when the age group older than 75 years was not excluded, except that the survival differences were more pronounced. Moreover, the proportion of patients adhering to therapeutic guidelines in our study is consistent with previous studies (approximately 74%) by the Optimizing the Surgical Treatment of Rectal Cancer (OSTRiCh) consortium.[15]

This study has several limitations. First, the large, national, retrospective database affords little control over locoregional practices such as different surgical techniques and chemotherapy and radiation regimens. We were unable to stratify outcomes by specific surgical techniques or quality of resection, but our exclusion criteria should have mitigated this limitation: we considered only transabdominal resections that had a negative surgical margin because an independent variable evaluating this (quality of the total mesorectal

excision dissection) does not exist in the NCDB. Controlling for chemotherapy regimens was also not possible; however, the majority of 5-flourouracil (5-FU)–based chemotherapy regimens used during the study period have resulted in similar long-term survival.[16] To investigate a time-dependent effect on the study findings from a possible national transition from 5-FU to folinic acid, fluorouracil, and oxaliplatin (FOLFOX) over the study period, the survival curves were recalculated for before and after 2008 (Supporting Fig. 4). Because the 2 major trials showing significant improvements in disease-free survival with the addition of oxaliplatin to 5-FU were published in 2007 and 2011,[17,18] we decided on 2008 as an appropriate time cutoff for the analysis. This showed no difference in the pre-2008 and post-2008 survival comparisons for the overall group (Supporting Fig. 4A) or for stage II and III patients (Supporting Fig. 4B,C). Regarding radiation regimens, studies with overlapping time periods have estimated long-course external-beam radiation to be used in more than 99% of the population,[19] and this is unlikely to have significantly affected our results. In addition, the number of patients excluded because of missing data, which amounts to approximately half of the stage I to III patients, is a limitation. Nevertheless, we have captured the largest number of patients to be studied in this manner to date.

A major limitation of this study is the absence of disease-free survival data in the NCDB. As a result, it may be difficult to show a distinction between an actuarial benefit of following NCCN guidelines and an age-driven difference in overall survival because of the low rate of mortality in the younger cohort. Certain subgroups within the younger cohort may benefit from following NCCN guidelines, and this could be a topic of further investigation. The absence of local recurrence and disease-free survival data in the NCDB also limits our ability to recognize the reason for poor survival among patients. However, overall survival and disease-free survival should more closely mirror each other for the younger population, and this makes these results more oncologically reliable in this age group. We attempted to overcome these limitations by excluding patients at a higher risk of mortality from age-based nononcologic causes. This included the exclusion of patients at the extremes of age (<20 and >75 years) and those who did not receive chemotherapy because of comorbidities and/or death before administration. Moreover, relative survival was calculated in addition to overall survival.

In summary, this study uses a large national cancer database to demonstrate that patients younger than 50 years diagnosed with rectal cancer represent a unique demographic group in which the survival advantage of receiving NCCN guideline–driven therapy for stage II and III disease does not materialize. Moreover, progressive age within this younger cohort is not a significant determinant of survival or a response to adjuvant therapies. This analysis supports the notion that early-onset rectal cancer may differ in its biology and response to therapy, as has been previously shown in colon cancer.[11] These data may help to stimulate future trial proposals to investigate the possibility of the exclusion or selective use of adjuvant therapies for stage II and III disease in the younger cohort to help to decrease treatment toxicity. We further provide age-specific survival data by decile for young patients. These data provide practicing physicians the ability to offer prognostic data tailored to the younger population, which do not exist at present and can greatly improve discussions with these patients regarding their long-term prognosis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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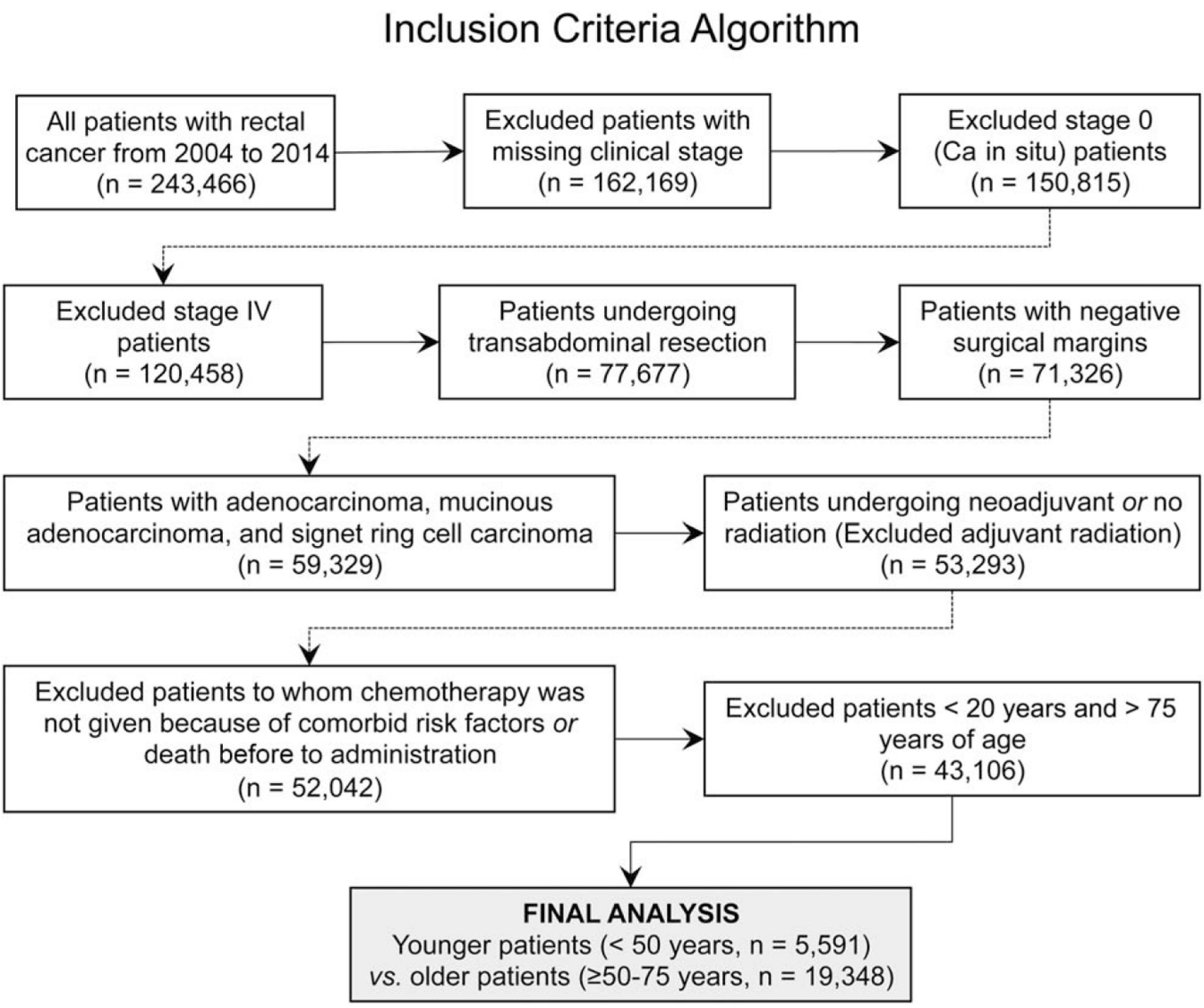


Figure 1.
Inclusion criteria algorithm. Ca indicates carcinoma.

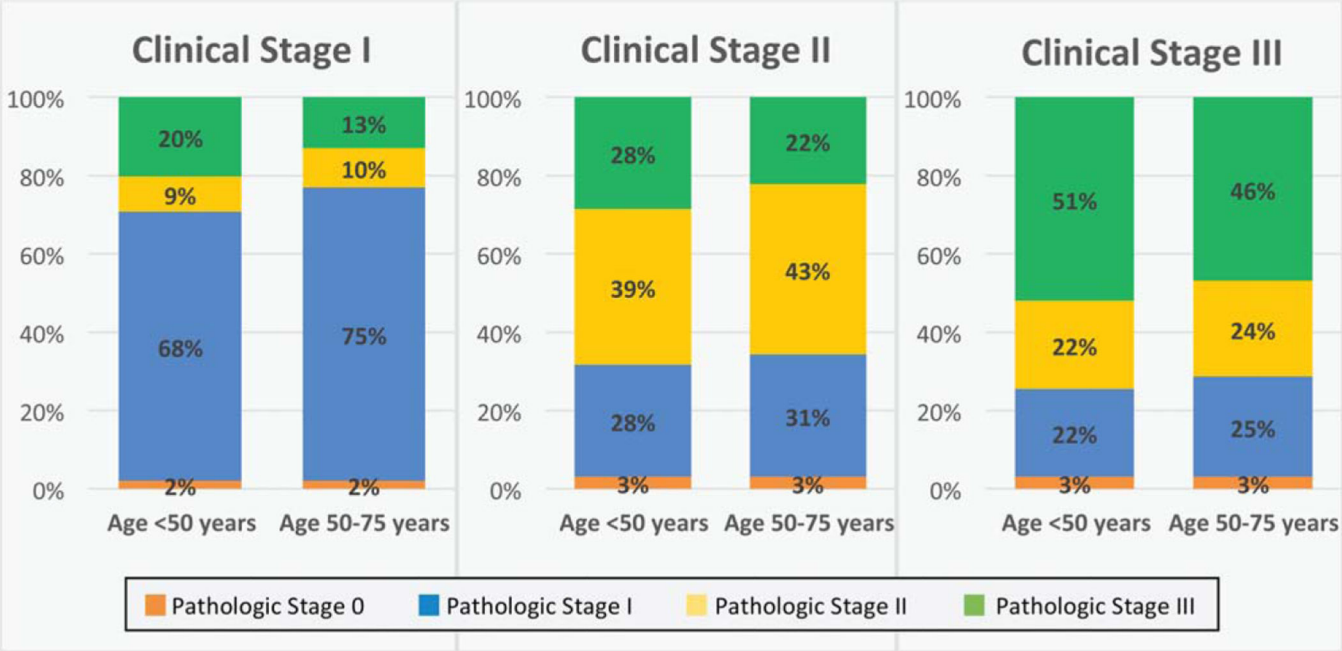


Figure 2.

Concordance of clinical and pathologic stages stratified by age and stage. No difference was noted across age cohorts; this signified equivalent accuracy of clinical staging across groups.

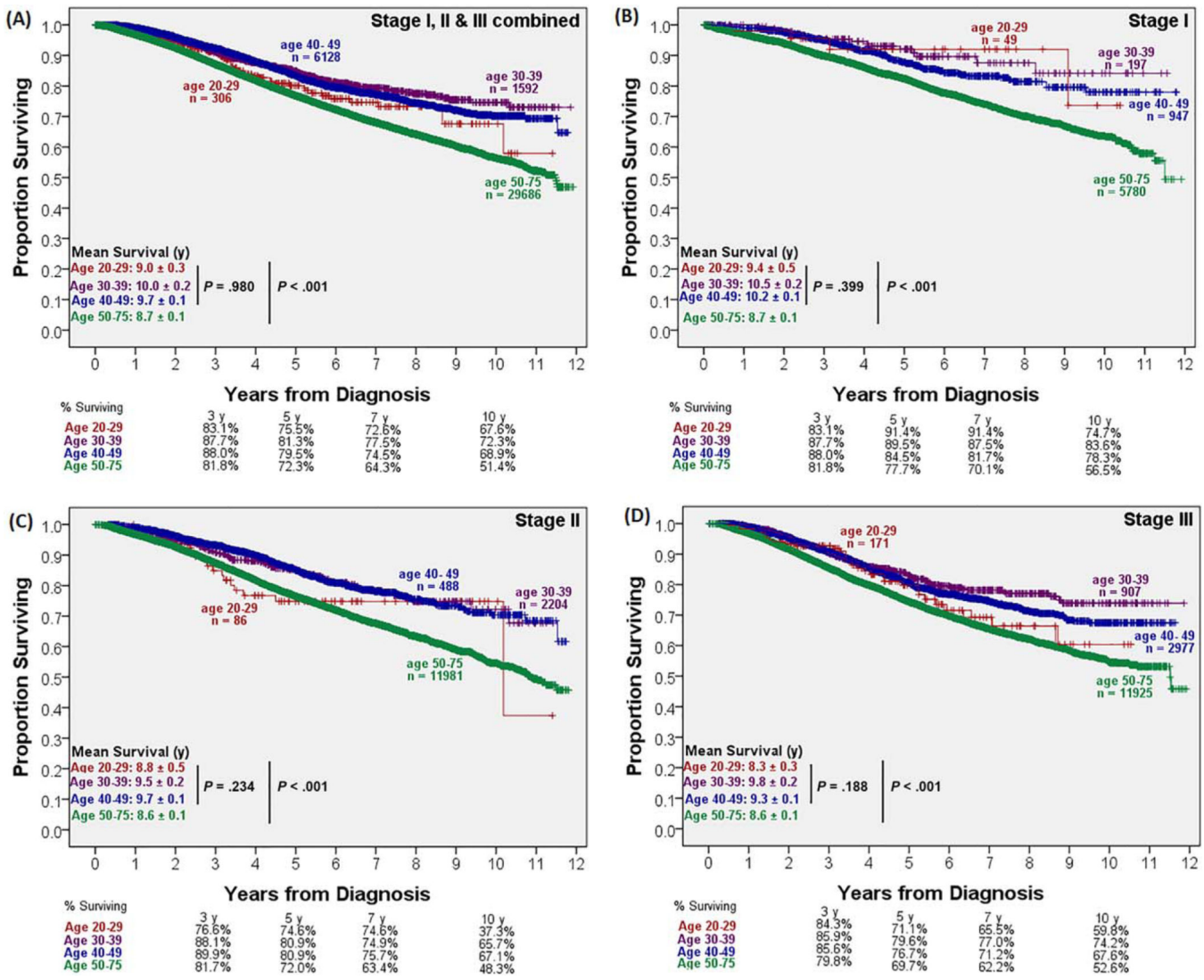
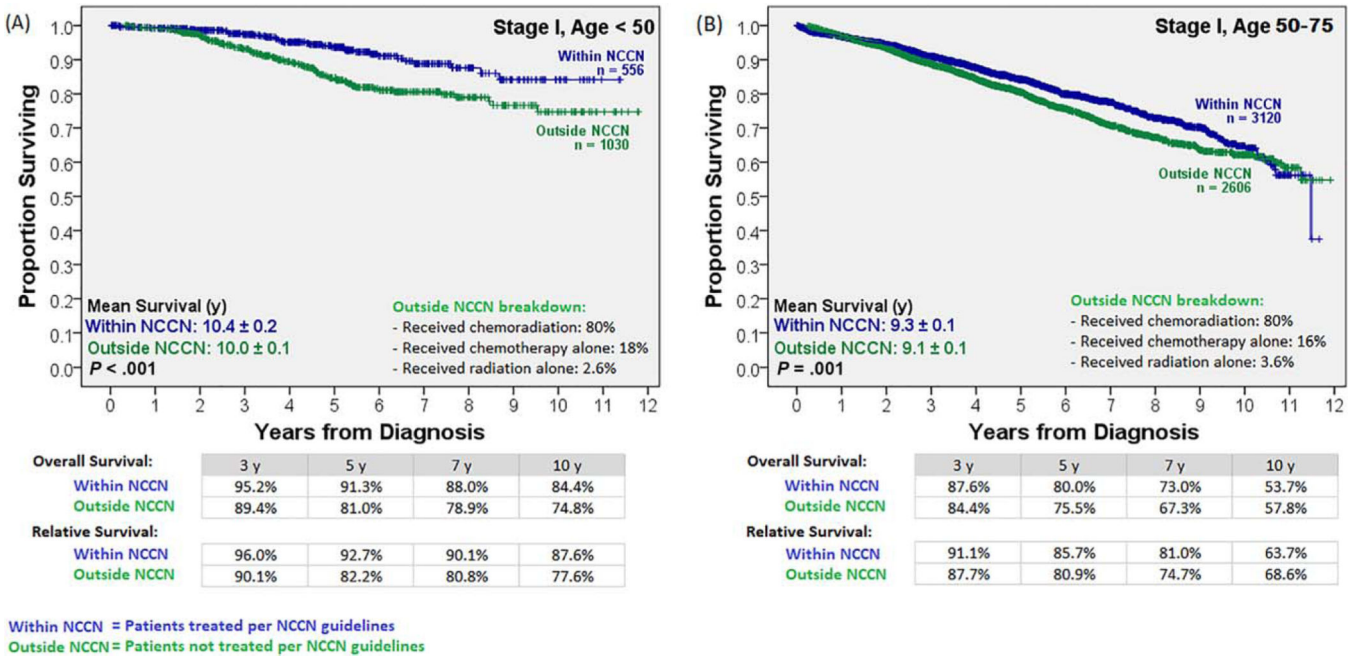


Figure 3.
Overall survival by age.



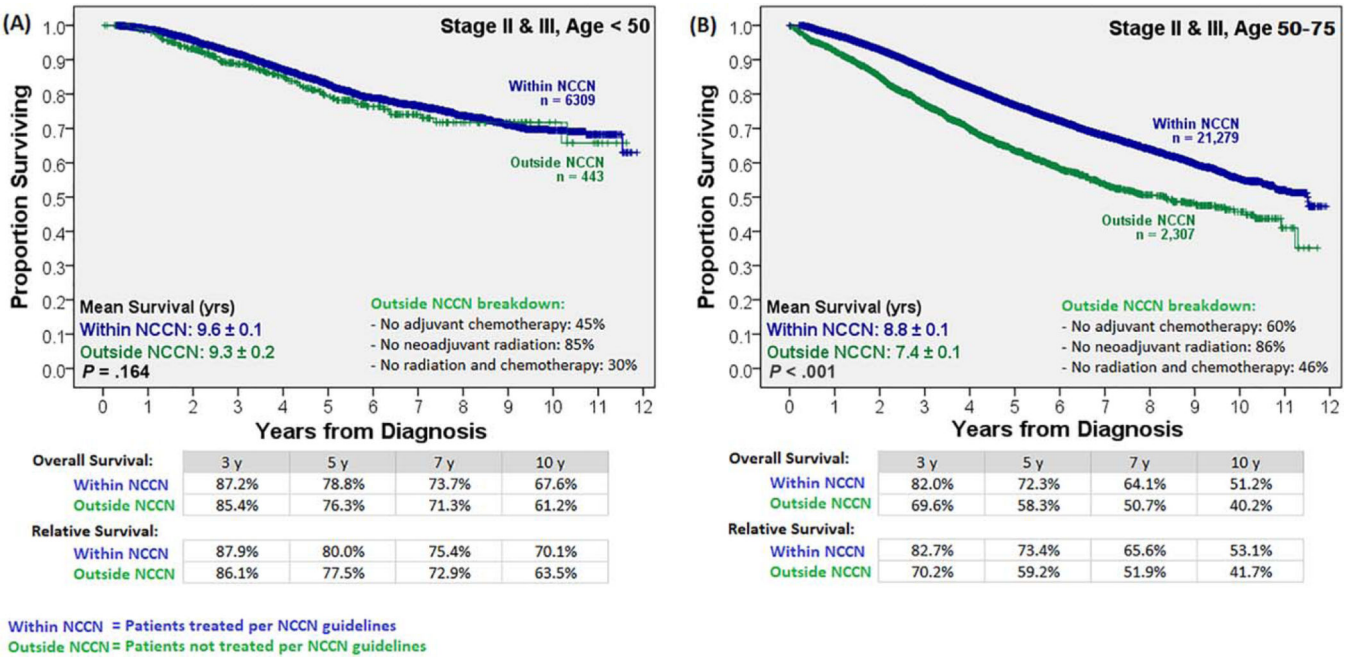
	3 y	5 y	7 y	10 y
Overall Survival:				
Within NCCN	95.2%	91.3%	88.0%	84.4%
Outside NCCN	89.4%	81.0%	78.9%	74.8%
Relative Survival:				
Within NCCN	96.0%	92.7%	90.1%	87.6%
Outside NCCN	90.1%	82.2%	80.8%	77.6%

	3 y	5 y	7 y	10 y
Overall Survival:				
Within NCCN	87.6%	80.0%	73.0%	53.7%
Outside NCCN	84.4%	75.5%	67.3%	57.8%
Relative Survival:				
Within NCCN	91.1%	85.7%	81.0%	63.7%
Outside NCCN	87.7%	80.9%	74.7%	68.6%

Within NCCN = Patients treated per NCCN guidelines
Outside NCCN = Patients not treated per NCCN guidelines

Figure 4.

Overall and relative survival with stage I disease stratified by age and treatment adherence to NCCN guidelines. A survival benefit was noted from following NCCN guideline–driven care in both age cohorts. NCCN indicates National Comprehensive Cancer Network.



Overall Survival:	3 y	5 y	7 y	10 y
Within NCCN	87.2%	78.8%	73.7%	67.6%
Outside NCCN	85.4%	76.3%	71.3%	61.2%
Relative Survival:				
Within NCCN	87.9%	80.0%	75.4%	70.1%
Outside NCCN	86.1%	77.5%	72.9%	63.5%

Overall Survival:	3 y	5 y	7 y	10 y
Within NCCN	82.0%	72.3%	64.1%	51.2%
Outside NCCN	69.6%	58.3%	50.7%	40.2%
Relative Survival:				
Within NCCN	82.7%	73.4%	65.6%	53.1%
Outside NCCN	70.2%	59.2%	51.9%	41.7%

Within NCCN = Patients treated per NCCN guidelines
Outside NCCN = Patients not treated per NCCN guidelines

Figure 5.

Overall and relative survival with clinical stage II and III disease stratified by age and chemoradiation therapy: Unlike their older counterparts, patients younger than 50 years showed no survival benefit from NCCN guideline–directed therapy. NCCN indicates National Comprehensive Cancer Network.

TABLE 1.

Age-Based Comparison of Clinicodemographic Data for Patients With Rectal Cancer

Characteristic	<50 y Old		50–75 y Old		*P*
	No.	% of Total	No.	% of Total	
Sex					
Male	5335	58.5	21,711	63.9	<.001[a]
Female	3791	41.5	12,269	36.1	
Race					
White	7626	85.5	29,429	87.9	<.001[b]
African American	838	9.4	2629	7.9	
Native American	43	0.5	164	0.5	
Asian/Pacific Islander	415	4.6	1245	3.7	
Spanish origin					
Non-Hispanic	7984	92.2	30,309	94.3	<.001[b]
Hispanic	677	7.8	1831	5.7	
Treatment site					
Community center	544	7.8	3200	9.4	<.001[c]
Comprehensive community center	2757	39.6	14,843	43.7	
Academic center	2900	41.7	12,394	36.5	
Integrated network	760	10.9	3543	10.4	
Insurance status					
Uninsured	590	6.6	1469	4.4	<.001[d]
Private/managed care	7022	78.2	17,555	52.4	
Medicaid	962	10.7	1991	5.9	
Medicare	283	3.2	12,080	36.0	
Other government	120	1.3	435	1.3	
Income level					
<$38,000/y	1385	15.3	5932	17.6	<.001[e]
$38,000–47,999/y	2037	22.5	8240	24.5	

Characteristic	<50 y Old		50–75 y Old		P
	No.	% of Total	No.	% of Total	
$48,000–62,999/y	2426	26.8	9197	27.3	
≥$63,000/y	3202	35.4	10,299	30.6	
Population density					
Urban	1294	14.6	5850	17.7	<.001[f]
Metro	7403	83.6	26,387	79.8	
Rural	160	1.8	838	25.8	
Charlson comorbidity score					
0	8202	89.9	26,330	77.5	<.001[g]
1	796	8.7	6147	18.1	
≥2	128	1.4	1503	4.4	
Stage at diagnosis					
I	2194	33.2	9586	39.1	<.001[h]
II	1756	26.6	7296	29.7	
III	2663	40.3	7656	31.2	
Tumor differentiation					
Well differentiated	657	8.3	2583	8.7	<.001[i]
Moderately differentiated	6178	77.7	23,391	79.0	
Poorly differentiated	1034	13.0	3362	11.3	
Undifferentiated, anaplastic	83	1.0	290	1.0	
Histology					
Adenocarcinoma	8521	93.4	32,130	94.6	<.001[j]
Mucinous	500	5.5	1677	4.9	
Signet ring cell	105	1.2	173	0.5	
Interval between diagnosis and start of treatment, mean ± SD, d	118.9 ± 0.6	—	117.3 ± 0.3	—	<.001
Interval between diagnosis and definitive surgery, mean ± SD, d	120.6 ± 0.3	—	122.1 ± 0.6	—	<.001

[a] The *P* value indicates that the younger cohort had a significantly higher proportion of females.

[b] The *P* value indicates that the younger cohort had a significantly higher proportion of minorities.

[c] The *P* value indicates that the younger cohort had a significantly higher proportion of patients treated at academic/integrated centers.

[d] The *P* value indicates that the younger cohort had a significantly higher proportion of uninsured patients.

[e] The *P* value indicates that the younger cohort had a significantly higher proportion of higher income earners.

[f] The *P* value indicates that the younger cohort had a significantly higher proportion of patients with a metropolitan residence.

[g] The *P* value indicates that the younger cohort had a significantly lower comorbidity index.

[h] The *P* value indicates that the younger cohort had a significantly higher proportion of patients with a greater stage at diagnosis.

[i] The *P* value indicates that the younger cohort had a significantly higher proportion of patients with undifferentiated or poorly differentiated lesions.

[j] The *P* value indicates that the younger cohort had a significantly higher proportion of patients with mucinous or signet ring cell lesions.

TABLE 2.

Age-Based Multivariate Analysis of Overall Mortality for Patients With Rectal Cancer

	<50 y Old			50–75 y Old		
Characteristic	**Hazard Ratio**	**95% CI**	***P***	**Hazard Ratio**	**95% CI**	***P***
Age (y)	1.01	0.98–1.04	NS	1.03	1.02–1.04	<.001
Sex: female (ref male)	0.70	0.59–0.84	<.001	0.80	0.75–0.87	<.001
Race (ref white)						
African American	1.11	0.83–1.48	NS	1.15	1.02–1.30	.028
Native American	1.53	0.61–3.83	NS	0.83	0.47–1.48	NS
Asian/Pacific Islander	0.86	0.55–1.35	NS	0.87	0.71–1.06	NS
Hispanic (ref non-Hispanic)	1.05	0.74–1.48	NS	0.86	0.72–1.01	NS
Treatment site (ref community center)						
Comprehensive community center	1.05	0.75–1.45	NS	0.93	0.83–1.04	NS
Academic center	0.89	0.64–1.23	NS	0.81	0.72–0.92	.001
Integrated network	1.00	0.67–1.47	NS	0.81	0.70–0.95	.007
Insurance status (ref private insurance)						
Uninsured	0.89	0.69–1.37	NS	1.47	1.25–1.74	<.001
Medicaid	1.60	1.24–2.07	<.001	1.44	1.23–1.67	<.001
Medicare	1.56	1.05–2.31	.026	1.23	1.11–1.36	<.001
Other government	1.06	0.43–2.56	NS	1.82	1.38–2.40	<.001
Income level (ref < $38,000/y)						
$38,000–47,999/y	0.97	0.74–1.27	NS	0.913	0.82–1.01	NS
$48,000–62,999/y	0.94	0.72–1.23	NS	0.835	0.75–0.93	.001
≥$63,000	0.66	0.49–0.87	.004	0.81	0.73–0.91	<.001
Population density (ref urban)						
Metro	0.99	0.78–1.26	NS	1.01	0.92–1.12	NS
Rural	0.67	0.35–1.27	NS	1.10	0.88–1.40	NS
Charlson comorbidity score (ref 0)						
1	1.10	0.82–1.47	NS	1.34	1.23–1.46	<.001
≥2	1.80	1.04–3.10	.008	2.11	1.84–2.41	<.001
Clinical stage at diagnosis: III (ref II)	1.02	0.84–1.23	NS	0.98	0.91–1.05	NS

Characteristic	<50 y Old			50–75 y Old		
	Hazard Ratio	95% CI	*P*	Hazard Ratio	95% CI	*P*
Pathologic stage at diagnosis (ref I)						
II	1.92	1.40–2.65	<.001	1.5	1.35–1.66	<.001
III	3.78	2.81–5.07	<.001	2.39	2.16–2.64	<.001
Tumor differentiation (ref well differentiated)						
Moderately differentiated	1.05	0.74–1.49	NS	0.944	0.83–1.08	NS
Poorly differentiated	1.55	1.04–2.30	<.001	1.37	1.17–1.59	<.001
Undifferentiated, anaplastic	1.52	0.70–3.30	NS	1.54	1.15–2.06	.004
Histology (ref adenocarcinoma)						
Mucinous	1.20	0.86–1.67	NS	1.05	0.91–1.20	NS
Signet ring cell	3.44	2.03–5.83	<.001	1.56	1.08–2.25	<.001
Neoadjuvant therapy for stage II/III (ref no neoadjuvant therapy)	1.11	0.60–1.42	NS	0.77	0.70–0.85	<.001

Abbreviations: CI, confidence interval; NS, not statistically significant ($P \geq .05$); Ref, reference variable for the multivariate analysis.