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Author
Latifi, Niloofar

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Niloofar Latifi*, Katherine E. Fero*, Anthony J. Paravati, Gregory M. Heestand, Lisa Parry, Sonia L Ramamoorthy, Samuel Eisenstein, Maria Elena Martinez, Daniel R Simpson, and James D. Murphy

Department of Radiation Medicine and Applied Sciences (NL, KEF, AJP, DRS, JDM), Hematology – Oncology, Department of Medicine (GEH), Colon and Rectal Surgery, Department of Surgery (LP, SLR, SE), and Department of Family & Preventive Medicine (MEM), University of California San Diego, La Jolla, CA

*These authors contributed equally to this work.

Correspondence to:
James D. Murphy, M.D., M.S.
University of California, San Diego
Department of Radiation Medicine and Applied Sciences
3960 Health Sciences Drive, MC0865
La Jolla, CA 92093-0865
Tel: 858-822-6080 / Fax: 858-246-1505 / email: j2murphy@ucsd.edu

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ABSTRACT

Background

The incidence of young-onset rectal cancer is increasing, and emerging evidence suggests younger patients have more aggressive disease. The standard of care for stage II and III rectal cancer includes neoadjuvant chemoradiotherapy followed by surgery and adjuvant chemotherapy. The purpose of this study was to determine whether response to neoadjuvant chemoradiotherapy differs in young-onset rectal cancer patients compared to older individuals.

Methods

We identified 26,681 patients within the National Cancer Database (NCDB) with stage II or III rectal adenocarcinoma diagnosed between 2004-2013. Response to treatment in the primary rectal tumor and lymph nodes were separately assessed by comparing pre-chemoradiotherapy clinical staging to post-chemoradiotherapy pathologic staging. Univariable and multivariable regression models were used to determine the influence of age on complete response rates, and determine whether the impact of treatment response on survival varied by patient age.

Results

The primary rectal tumor complete response rate did not vary by patient age, whereas the odds of a complete nodal response decreased by 36% for patients 18-39 compared to those over 70 (odds ratio 0.64; 95% CI0.531-0.781). A complete response within the primary rectal tumor reduced the risk of death among patients 18-39 years old by 59%, compared to 26% for those over 70. A complete response within the lymph nodes reduced the risk of death among patients 18-39 years old by 68%, compared to 38% for those over 70.

Conclusions

Patients with young-onset rectal cancer were less likely to respond to chemoradiotherapy, though young responders experience a greater survival benefit. Understanding this age-dependent treatment response will help when discussing prognosis with patients, and adds support to evidence that suggests different disease biology with young-onset rectal cancer.

INTRODUCTION

The incidence of rectal cancer among young adults has doubled over the past three decades.[1] By 2030, the projected incidence of rectal cancer among adults between 35 and 49 will increase by another 50%, and the incidence among those between 20 and 34 will more than double.[2] Increasing evidence suggests that the biology of rectal cancer differs in younger patients, with more aggressive histologic features, and an increased likelihood of regional lymph node involvement. [1,3,4] The increasing incidence and distinct presentation of young onset rectal cancer leads to the question of whether conventional treatment strategies are effective in this younger population.

The standard treatment approach to stage II and III rectal adenocarcinoma involves neoadjuvant chemoradiotherapy followed by surgical resection, then adjuvant chemotherapy.[5] The landmark trials that defined the standard of care in rectal cancer primarily involved older patients given that the median age of colorectal cancer diagnosis is 68.[6] Multiple studies demonstrate that response to chemoradiotherapy as assessed by pathology from surgery represents a key prognostic factor; specifically patients who have no evidence of residual disease after chemoradiation have a substantially reduced risk of rectal cancer mortality.[7,8] Furthermore, more recent studies report on strategies that use treatment response as a decision point to help guide the use of additional therapy such as surgery or adjuvant chemotherapy.[9,10]

The response to chemoradiotherapy in rectal cancer has important prognostic and potentially predictive capability, however research has not evaluated whether response to chemoradiotherapy varies by patient age. With more aggressive tumor biology among young adults one could hypothesize that young-onset rectal cancer patients might respond differently to treatment. The purpose of this study was to determine whether treatment response with neoadjuvant chemoradiotherapy differs among young-onset rectal cancer patients, and furthermore to determine whether the prognostic impact of treatment response varies across different age cohorts.

METHODS

Data Source

We conducted a retrospective cohort study utilizing the de-identified National Cancer Database (NCDB). The NCDB is a database jointly administered by the American College of Surgeons and the American Cancer Society. The NCDB covers the entire United States accounting for ~70% of newly diagnosed cancer cases reported from over 1,500 Commissions On Cancer accredited facilities.[11] The NCDB captures Information on individual patients including clinical, and demographic characteristics, as well as details about treatment and overall survival.

Study Population

The study population was restricted to patients ages 18 and older with clinical stage II or III rectal adenocarcinoma diagnosed between 2004 and 2013. The following International Classification of Diseases (ICD)-O-3 histology codes were used to identify patients with rectal adenocarcinoma: 8140–8148, 8200, 8260–8263, and 8480–8496. We restricted our analysis to patients who underwent neoadjuvant chemoradiation followed by surgical resection. The delivery of concurrent chemoradiation is not explicitly recorded within the NCDB, therefore we assumed patients received concurrent chemoradiation if the start dates of chemotherapy and radiation occurred within 14 days of one another. We included only patients with complete (non-missing) staging information. The final study population included 26,681 subjects, and the complete study cohort selection schema is shown in **Figure 1**.

Study Covariates

The following patient demographic and clinical covariables were extracted from the NCDB: age at diagnosis, sex, race, ethnicity, geographic region, median household income, type of health insurance, baseline Charlson comorbidity score, and year of cancer diagnosis. Tumor characteristics included the histologic grade, pre-treatment clinical tumor stage, and pathologic stage from surgery. We included additional treatment-specific variables known to influence response to chemoradiation including the radiation dose received, and time between radiation and surgical resection.[12] Additionally, we included the number of lymph nodes examined during surgery to help account for age-specific differences in lymph node dissections demonstrated in prior research. [13]

Study Endpoints

Younger patients present with a higher lymph node burden than older patients[13], and therefore we hypothesized that the response to chemoradiotherapy might differ between the primary rectal tumor and lymph nodes. Therefore we opted to analyze treatment response separately for the primary tumor and regional lymph nodes. A *primary tumor complete response* was defined from surgical pathology as the absence of tumor within the rectum (pT0/pTis/pTx). A *lymph node complete response* was defined as the absence of tumor within regional lymph nodes (pN0/pNx). The notation 'x' in pathology reports (pTx or pNx) indicates that the tumor or nodes could not be assessed.[14] To remain consistent with prior research we included these pTx and pNx patients in our definitions of pathologic response.[12] Additionally, we performed a sensitivity analysis excluding these patients (pTx and pNx) from our analysis which did not substantially influence our results (data not shown).

Analysis

Patient demographic, clinical, and treatment characteristics are reported as categorical variables as demonstrated in **Table 1**. Patient age at diagnosis was categorized into 10 year bins. Because of low numbers we grouped all patients under 40 in a single group, and all patients over 70 in a single group. Differences in patient, tumor and treatment characteristics across age groups were assessed with chi-squared tests. When analyzing the primary tumor response we included the entire study cohort (n=26,261), whereas when analyzing the lymph node response we included only those with lymph node involvement prior to chemoradiation (n=13,929). We use multivariable logistic regression models to evaluate the impact of patient age on treatment response while adjusting for confounding demographic, clinical and treatment variables. Covariates in our multivariable models were defined *a priori* based on factors that could affect a patient's response to neoadjuvant chemoradiation and are demonstrated in **Table 1**. We hypothesized that surgery and pathology practices could vary by treating institution, and differences in surgical techniques or pathology processing could introduce institution bias and thus influence the study endpoint of treatment response. NCDB does not disclose the treating institution, however they do record the reporting facility. To help reduce the potential impact of treatment institution bias we stratified our multivariable models by reporting facility.

We assessed whether the prognostic impact of treatment response varied among different age groups with multivariable Cox proportional hazard models with overall survival as the endpoint. We expected that age and response to treatment would each independently influence overall survival, though to understand whether the impact of treatment response differed among age groups we evaluated the statistical interaction between age and treatment response. Our multivariable survival models included the variables listed in **Table 1**, as well as age, response to treatment, and the interaction between age and response to treatment. Information on survival is only available for patients diagnosed through 2012, therefore those diagnosed in 2013 were not included in the survival analysis. All statistical tests performed were 2-sided; $P<.05$ was considered significant. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

RESULTS

Among the 26,681 patients in this study 5,714 (21%) were under the age of 50 at diagnosis. Patient characteristics are summarized in **Table 1**. In general younger patients with rectal cancer were slightly more likely to be female, non-White, Hispanic, and have a higher median household income. Younger patients tended to present with clinical T1/T2 tumors as opposed to T3/T4 tumors. Younger patients were also more likely to present with more advanced nodal disease, and have poorly or undifferentiated tumors. Younger patients were more likely to undergo extensive lymph node dissections during surgery, and receive higher radiation doses.

Figure 2 demonstrates the response to chemoradiotherapy grouped by patient age. The primary rectal tumor complete response rates did not vary by patient age, and ranged from 22-25% across all age groups. The lymph node complete response rates varied by patient age, and the rate decreased steadily from 65% for patients over 70 down to 53% for patients 18-39. Multivariable logistic regression that controled for potentially confounding factors found similar results to the unadjusted analysis (**Figure 3**). Specifically we found that the primary tumor complete response rates did not vary by patient age, whereas the probability of a lymph node complete response decreased with younger patients. The odds of a complete nodal response decreased by 36% for patients 18-39 compared to those over 70 (adjusted odds ratio 0.64; 95% CI 0.53-0.78). The complete multivariable analyses are reported in **Supplemental Table 1.**

Next, we examined whether the prognostic impact of treatment response varied by age. We found that the survival benefit for achieving a pathologic complete response in either the primary tumor or lymph nodes was greater among young patients compared to older patients (**Figure 4**). Achieving a primary tumor complete response reduced the risk of death among patients 18-39 years old by 59% (hazard ratio [HR] 0.41; 95% CI 0.27-0.63) compared to 26% for those 70+ (HR 0.74; 95% CI 0.66-0.82). Achieving a lymph node complete response reduced the risk of death among patients 18-39 years old by 68% (HR 0.32; 95% CI 0.21-0.47), compared to 38% for those 70+ (HR 0.62; 95% CI 0.54-0.71). Complete results of this analysis are reported in **Supplemental Table 2.**

DISCUSSION

The standard of care for Stage II and III rectal cancer consists of neoadjuvant chemotherapy with radiation treatment followed by surgical resection. This trimodality approach comes in large part from the findings of the German rectal cancer study comparing preoperative to postoperative chemoradiotherapy. This study found that, compared to postoperative chemoradiotherapy, neoadjuvant chemoradiotherapy reduced the risk of local tumor recurrence, reduced toxicity, and down-staged the tumor which led to improved rates of sphincter preserving surgery.[15] Only 8% of subjects receiving preoperative chemoradiotherapy in the German rectal study experienced a complete pathologic response, though the rates of complete response vary in the literature, ranging from 0 to 30 % or higher.[16-19] Multiple studies demonstrate that greater downstaging from chemoradiotherapy correlates with decreased risks of tumor recurrence and improved survival.[7,8] To our knowledge, this report represents the first analysis looking at how outcomes after neoadjuvant chemoradiotherapy differs by patient age. Given the increasing incidence of young-onset rectal cancer understanding how this disease differs from older adults will become increasingly important to optimally manage this subset of unique patients.

A key finding of this study relates to the observation that involved lymph nodes in young-onset rectal cancer patients appear more resistant to chemoradiation than involved nodes in older patients. Other studies demonstrate that younger rectal cancer patients have an increased risk of lymph node involvement at presentation.[13] Our study furthers this lymph node narrative by demonstrating that younger patients have a

36% decreased odds of achieving a complete lymph node response after treatment compared to older patients. Increased rates of lymph node involvement and resistance of lymph nodes to conventional chemoradiotherapy appear to represent a central theme of early onset rectal cancer.

A second important finding in this study relates to the survival benefit of a complete response to chemoradiation among young-onset rectal cancer patients. Response to chemoradiotherapy represents an accepted prognostic factor associated with improved survival in rectal cancer.[7,8] Our study demonstrates that the prognostic importance of a complete response in young patients surpasses the benefits of a complete response in older patients. Specifically, achieving a complete response within the primary tumor or lymph nodes reduces the risk of death among younger patients by 59% and 68%, respectively. The improved survival among young responders stands in contrast to the decreased overall response to chemoradiotherapy. Taken together the clinical findings in this study support the increasing evidence that the biology of young onset rectal cancer differs from older patients with this disease.

The findings in this study raise the important question of what tumor-specific factors in younger patients drive the differential response to treatment. Of colorectal patients under fifty nearly 20% arise from genetic syndromes, most commonly due to DNA mismatch repair.[20] Non-genetic syndrome colorectal cancers in younger patients may carry distinct molecular profiles with studies demonstrating higher rates of diploid microsatellite stable tumors[21], as well as lower rates of KRAS and BRAF mutations.[22] Understanding tumor- and host-related factors that influence the behavior of young-onset colorectal cancer will require carefully designed genetic epidemiology research in the future.

While this current study is the first to evaluate the impact of age on response to neoadjuvant therapy, others have evaluated the efficacy of adjuvant chemotherapy across different age groups. Multiple analyses demonstrate that the benefits of adding oxaliplatin to standard 5-FU based adjuvant chemotherapy diminish among elderly patients.[23-25] Whether this age-related difference with oxaliplatin stems from increased toxicity among older patients or differences in tumor biology remains an open question. Current clinical trials include a minority of patients with young-onset colorectal cancer, likely on the order of 15% of our clinical trial participants.[26] Conducting trials solely among young-adult colorectal cancer patients would likely prove difficult, though future clinical research should continue to prospectively assess the interaction between age and treatment outcome.

This study has limitations worth noting. One important consideration relates to the lack of standardization with surgery and pathology assessment. Any age-dependent differences in surgery (such as more extensive resection) or pathology processing (more detailed assessment) would likely lead to increased likelihood in finding residual tumor on surgical pathology after chemoradiation. Our analysis controlled for number of resected lymph nodes which likely correlates with extensiveness of surgery, and also stratified by reporting center to reduce the impact of institution bias. Despite these corrective efforts, residual confounding remains a possibility. Other limitations relate to the potential for bias due to unmeasured confounders. The NCDB does not collect detailed information about the specific chemotherapy agent or doses and schedules. We assume the majority of patients would receive 5-FU based chemotherapy concurrently with radiation, though we cannot confirm this assumption. Any age-related variation in concurrent chemotherapy delivery could potentially influence our findings. Additionally, we lack information on cancer-specific survival, therefore we cannot account for the competing risk of non-cancer death. While our multivariable models control for patient age and comorbidity, both of which serve as surrogates for non-cancer death, the attenuated prognostic impact of a complete response in older patients may partly arise from the residual competing risk of non-cancer death.

In conclusion, this study adds to increasing evidence that young-onset rectal cancer may represent a distinct clinical entity.[27] Younger patients have an increased likelihood of nodal involvement on presentation, and are less likely to achieve a complete pathologic response after neoadjuvant chemoradiotherapy. Furthermore, younger rectal cancer patients who achieve a complete response to treatment experience a greater survival

benefit than their older counterparts. This age-dependent response to treatment will help when counseling patients and assessing risk of disease progression among rectal cancer patients.

Tables and Figures

Table 1. Demographic and clinical characteristics, by age group. Comparisons of proportion of patients were performed with Chi-square tests, comparison of average time between radiation and surgery performed with one-way ANOVA.

		AGE GROUP					
Variables	**Total Cohort (N)**	**18-39 (%)**	**40-49 (%)**	**50-59 (%)**	**60-69 (%)**	**70+ (%)**	**P Value**
Number	26,681	1,387	4,326	7,952	7,424	5,591	
Sex							
Male	16,749	57.8	60.0	64.7	65.5	59.0	<0.001
Female	9,932	42.2	39.0	35.3	34.3	41.0	
Race							
White	23,140	84.4	84.2	85.3	87.8	89.8	
Black	2,090	8.7	9.7	9.0	6.9	5.7	<0.001
Other/Unknown	1,451	6.9	6.1	5.7	5.3	4.5	
Insurance							
Medicaid	1,732	13.3	9.9	8.9	4.4	1.6	
Medicare	8,761	2.0	4.0	5.5	44.3	86.4	<0.001
Private Insurance	14,164	73.6	76.4	75.2	44.5	10.0	
Other/Unknown	2,024	11.1	9.8	10.5	6.8	2.0	
National Origin							
Hispanic	1,378	7.7	6.2	5.7	4.6	3.6	
Non- Hispanic	23,597	86.7	87.6	87.6	89.7	89.1	<0.001
Unknown	1,706	5.6	6.2	6.7	5.7	7.3	
Median Income							
Bottom Quartile	4,797	16.7	16.9	18.7	18.1	17.9	
Second Quartile	6,682	25.4	22.5	24.6	26.0	26.3	
Third Quartile	7,274	27.2	27.4	27.0	27.3	27.5	<0.001
Fourth Quartile	7,928	30.7	33.2	29.7	28.6	28.3	
Year of diagnosis							
2004	1,604	6.0	5.6	5.6	5.9	6.5	
2005	1,842	6.2	6.5	6.8	7.3	7.1	
2006	2,024	8.1	7.5	7.7	7.3	7.7	
2007	2,314	8.9	9.1	8.2	8.6	9.1	
2008	2,827	10.9	11.3	10.6	10.1	10.7	0.49
2009	2,986	12.0	11.7	10.9	11.0	11.4	
2010	3,133	12.5	11.8	11.8	11.9	11.2	
2011	3,229	12.0	12.0	12.06	12.2	12.2	
2012	3,311	12.0	11.7	12.7	12.8	12.3	
2013	3,411	11.4	12.7	13.48	13.0	11.9	
Clinical T stage							
T1	236	1.2	1.3	0.9	0.8	0.6	
T2	1,236	6.2	5.7	4.9	4.4	3.3	<0.001
T3	23,130	83.7	85.7	86.1	86.8	89.0	
T4	2,079	8.9	7.3	8.1	8.0	7.15	
Clinical Nodal stage							
N0	12,752	34.6	41.8	46.0	50.1	55.2	
N1	12,082	54.0	49.1	46.7	43.6	40.2	<0.001
N2	1,847	11.4	9.0	7.2	6.3	4.6	
Lymph nodes examined							
1-5	3,103	7.2	8.3	11.2	12.3	15.0	
6-10	5,762	14.6	18.9	21.2	23.3	23.7	
11-15	8,293	27.1	31.7	31.5	31.2	30.9	<0.001
16-20	5,115	23.4	20.3	20.0	18.6	17.0	
20+	4,408	27.7	20.8	16.2	14.6	13.4	
Tumor Grade							
Well differentiated	1,869	5.9	6.4	6.6	7.7	7.4	
Moderate differentiated	18,013	64.7	67.6	68.7	67.5	66.6	

Poorly differentiated	3,044	15.0	12.4	11.0	10.6	11.5	<0.001
Undifferentiated	270	1.7	1.1	1.1	0.88	0.91	
Unknown	3,485	12.7	12.6	12.8	13.4	13.6	
Charlson Score							
0	21,434	93.5	89.0	83.4	75.8	72.1	
1	4,306	6.2	9.7	14.2	19.8	21.5	<0.001
2	941	0.29	1.34	2.49	4.38	6.37	
Total Radiation dose (cGy)							
≤ 4500	4,813	15.6	17.8	16.6	18.2	20.7	
4501 - 5040	15,482	58.9	57.2	59.1	57.7	57.4	<0.001
>5040	3,431	13.3	13.1	13.5	13.0	11.6	
Unknown	2,955	12.3	12.0	10.8	11.2	10.3	
Days from radiation to surgery – mean (SD)	97 (24)	95 (21)	95 (23)	97 (24)	97 (24)	98 (26)	<0.001

Figure 1. Patient selection criteria.

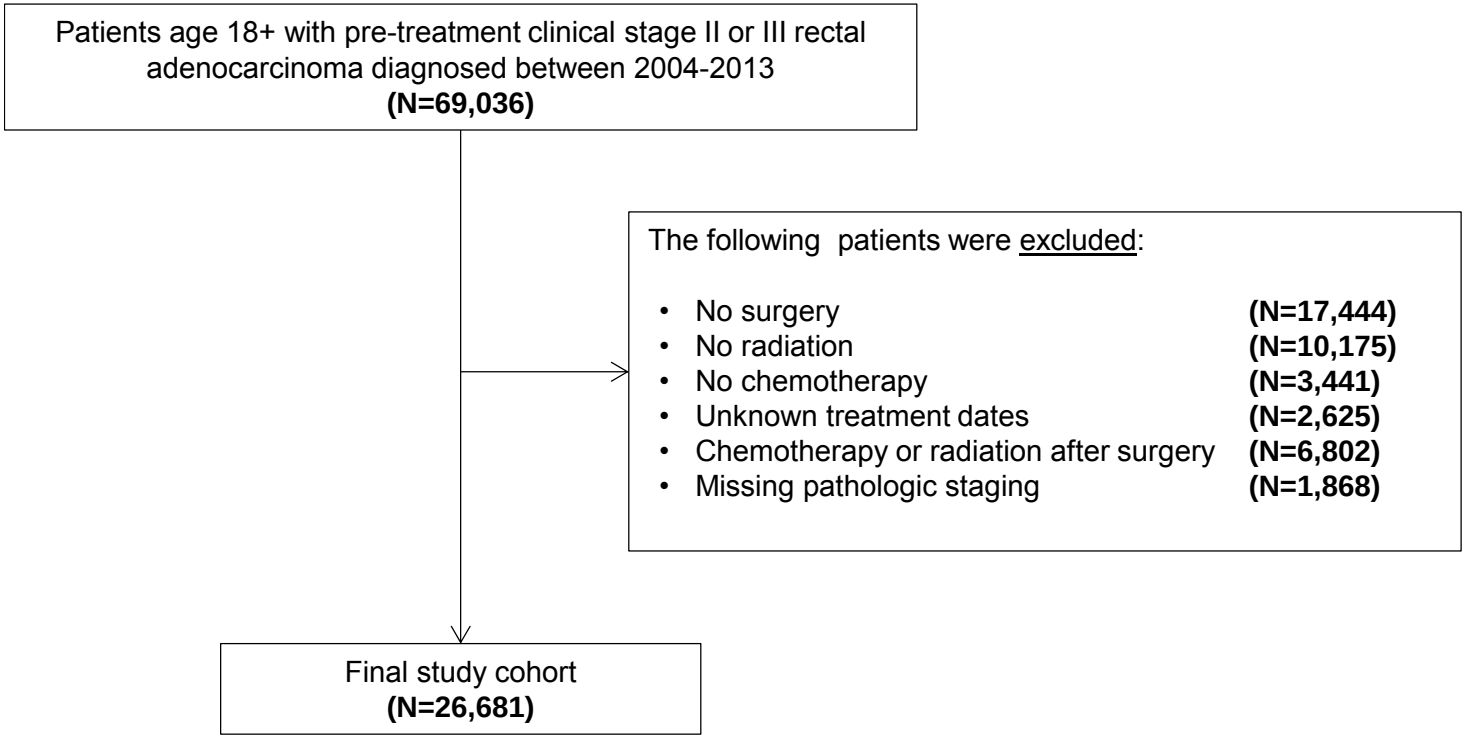
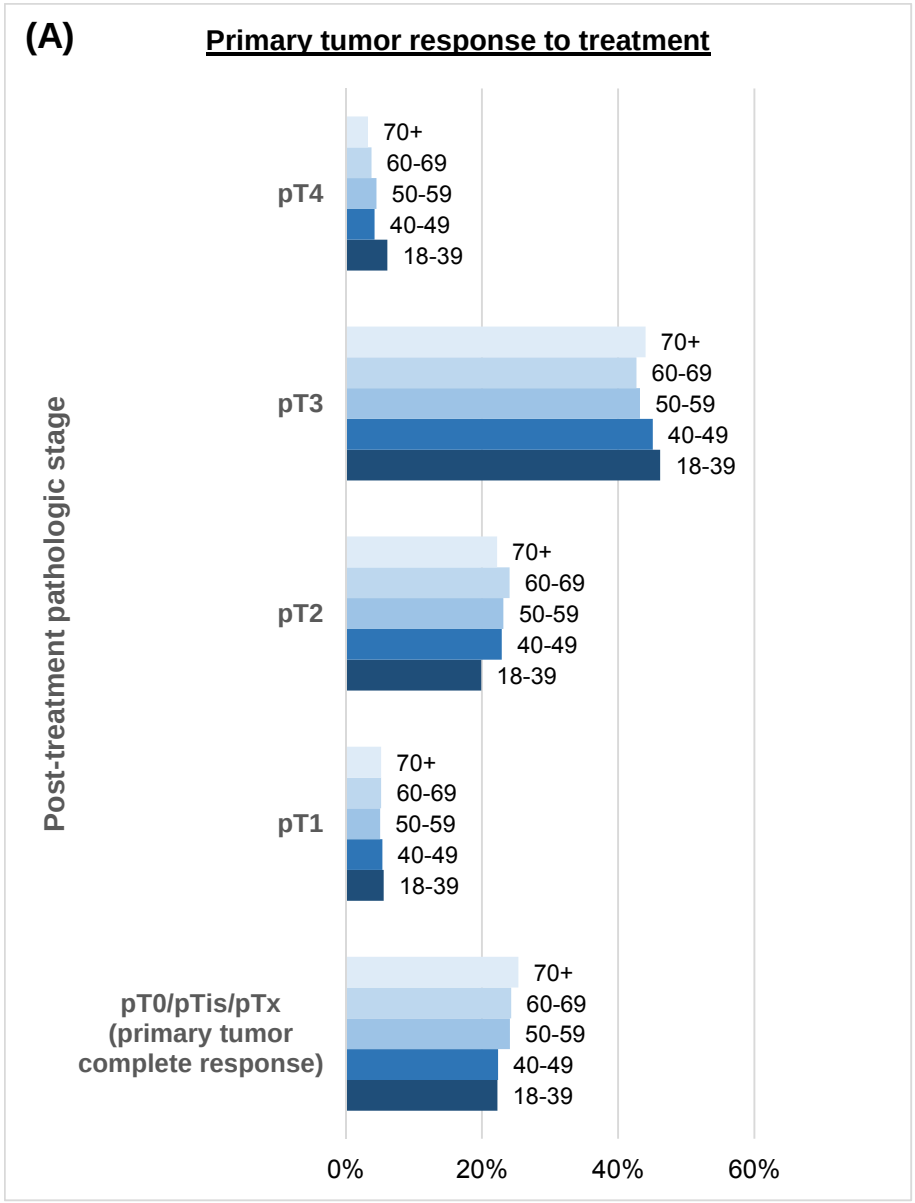


Figure 2. This figure demonstrates the response to neoadjuvant chemoradiotherapy stratified by age among rectal cancer patients within the National Cancer Database. Panel A demonstrates the primary rectal tumor treatment response among the whole study cohort (n=26,681), and panel B represents the regional lymph node response among patients with initial lymph node involvement (n=13,929).



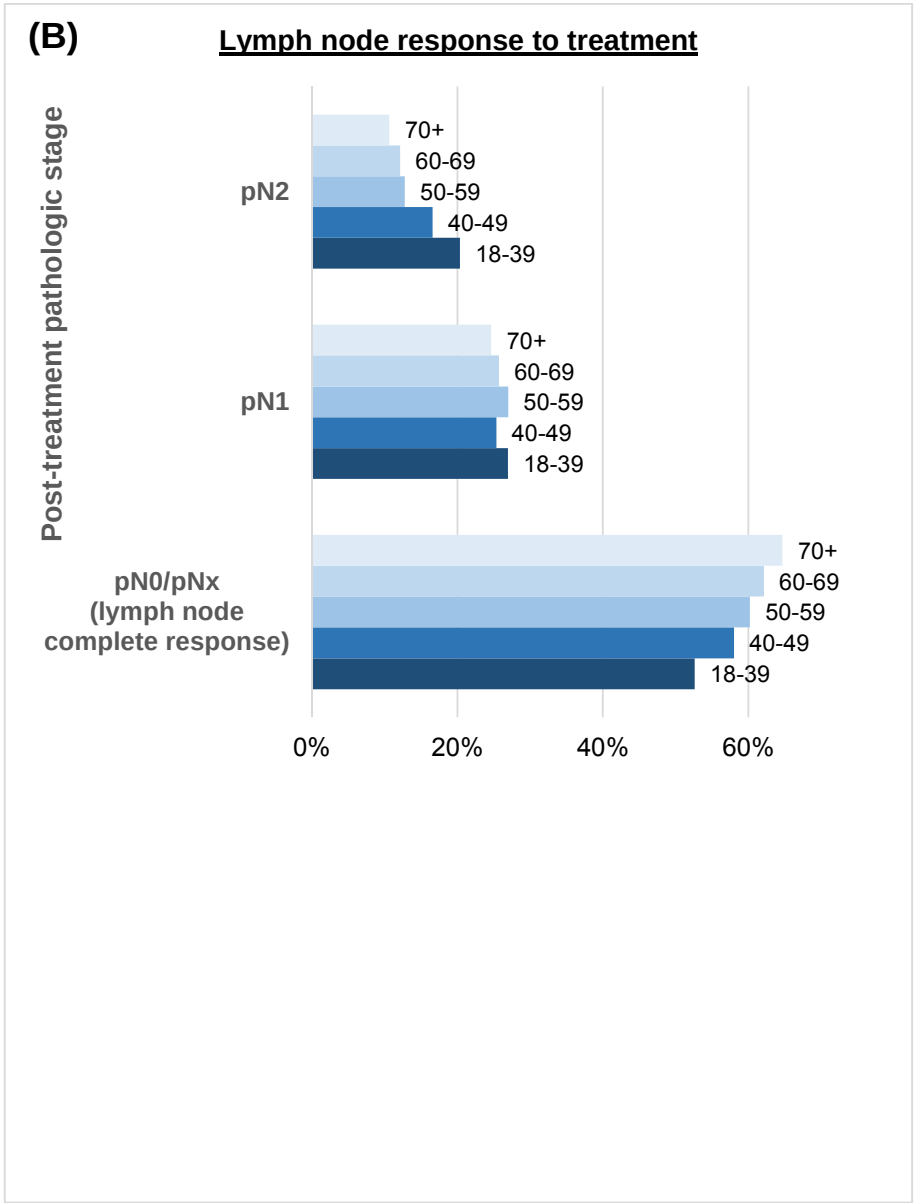


Figure 3. This figure represents the results of a multivariable logistic regression that determines the impact of age on compete treatment response to neoadjuvant chemoradiotherapy. The plot shows the adjusted odds ratio of achieving a primary tumor complete response (left), and a complete lymph node response (right) while controlling for factors including age, race, ethnicity, insurance type, median income, Charlson score, pre-treatment clinical T stage, pre-treatment clinical N stage, tumor grade, number of lymph nodes examined, time between radiation and surgery, total radiation dose, and year of diagnosis.

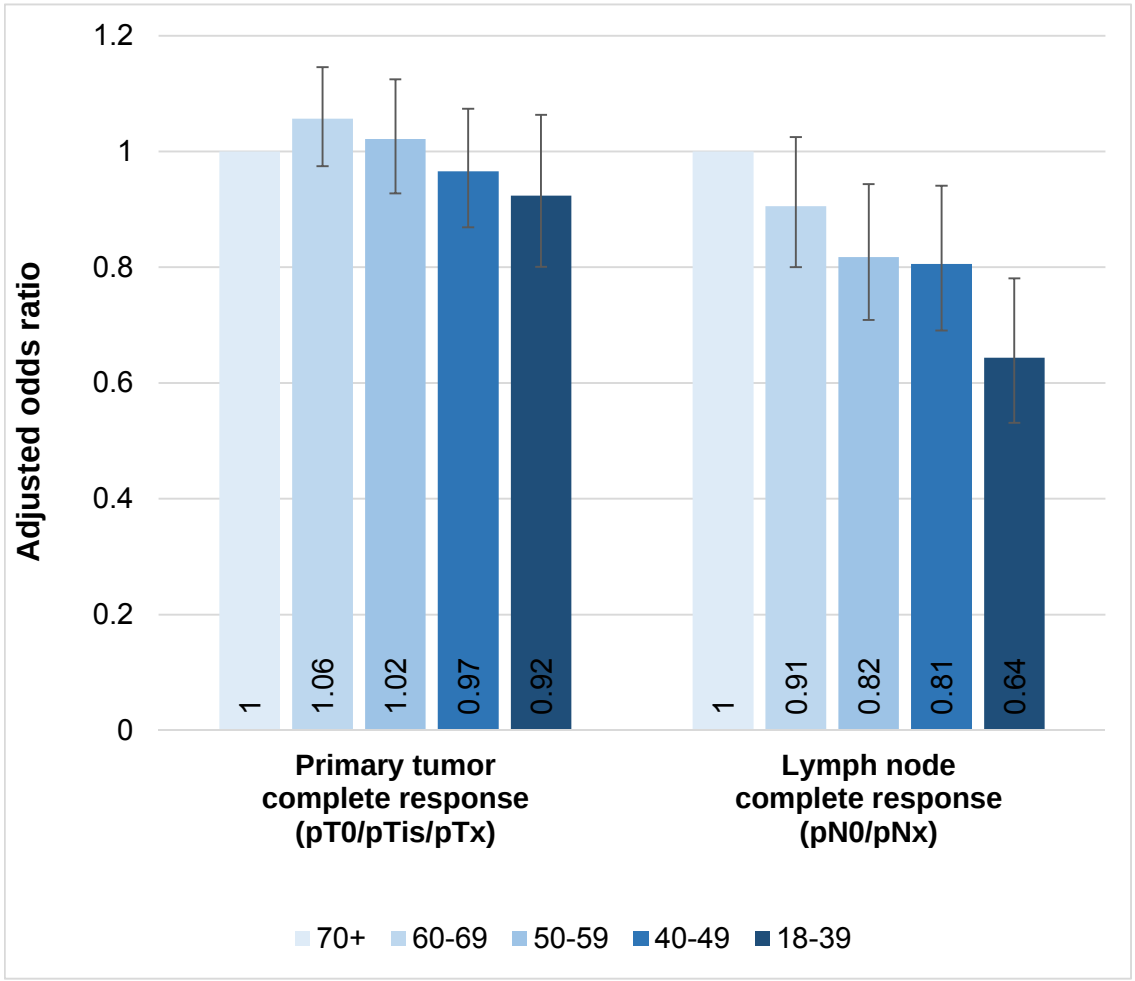
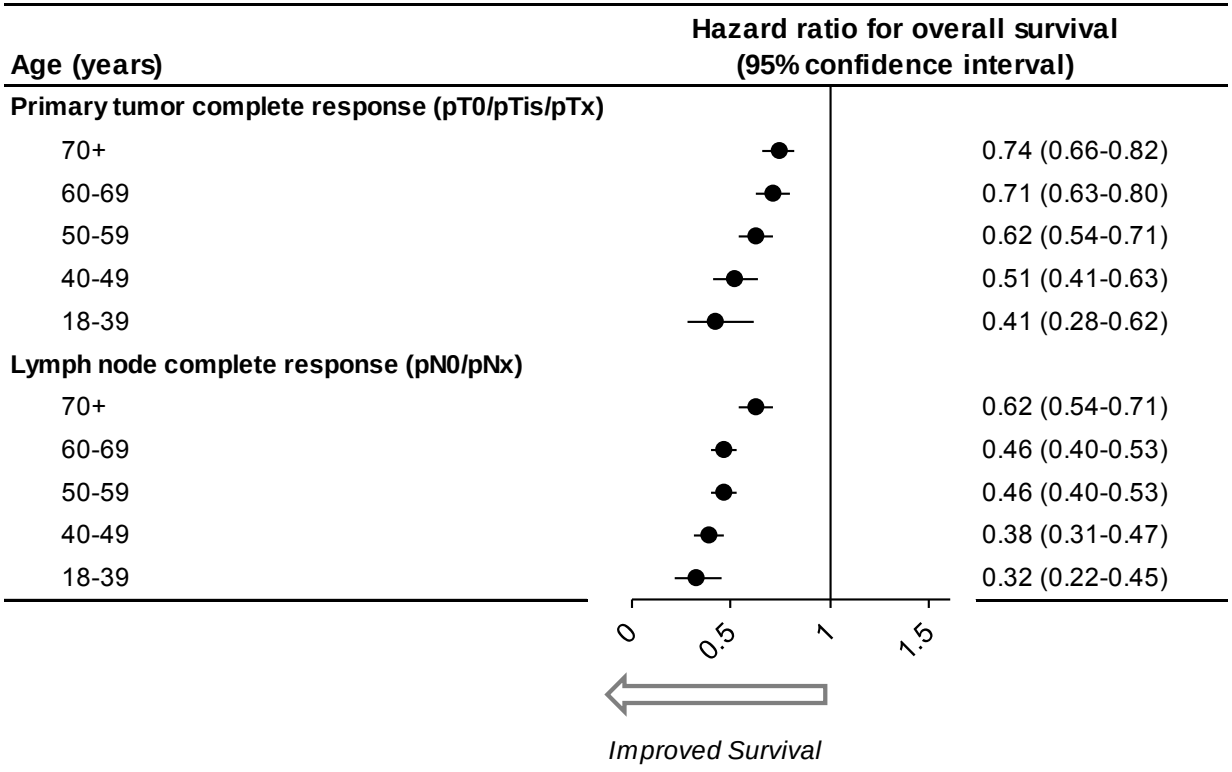


Figure 4. This forest plot demonstrates a multivariable Cox regression analysis to assess the impact of age on the survival benefit conferred by a primary rectal tumor complete response and a lymph node complete response. Dots represent the hazard ratios for overall survival and error bars represent 95% confidence intervals. The multivariable regression adjusted for race, ethnicity, insurance type, median income, Charlson score, clinical T stage, clinical N stage, histologic grade, number of lymph nodes examined, time between radiation and surgery, total radiation dose, and year of diagnosis.



SUPPLEMENTARY MATERIAL

Supplemental Table 1. The following table represents the results of the full multivariable logistic regression models to identify predictors of a primary tumor complete response (pT0/pTis/pTx), and a lymph node complete response (pN0/pNx). The analysis of primary tumor complete response included the whole study cohort, and the analysis of lymph node complete response included only those with nodal involvement at diagnosis.

	Pathologic Response OR [95%CI]	
Characteristic	**Primary rectal complete response (pT0/pTis/pTx)**	**Lymph node complete response (pN0/pNx)**
Age (years)		
18-39	0.924 [0.801-1.064]	0.644 [0.531-0.781]
40-49	0.966 [0.869-1.074]	0.806 [0.691-0.941]
50-59	1.022 [0.928-1.125]	0.818 [0.709-0.944]
60-69	1.057 [0.975-1.146]	0.906 [0.800-1.025]
70+	Ref	Ref
Sex		
Male	1.013 [0.961-1.069]	1.076 [0.998-1.162]
Female	Ref	Ref
Race		
White	Ref	Ref
Black	0.924 [0.834-1.025]	0.866 [0.749-1.001]
Unknown	0.961 [0.85-1.086]	0.84 [0.707-0.999]
Ethnicity		
Non-Hispanic	0.908 [0.793-1.041]	0.831 [0.683-1.011]
Hispanic	0.89 [0.739-1.07]	0.905 [0.696-1.177]
Other	Ref	Ref
Insurance		
Private	Ref	Ref
Medicare	0.949 [0.878-1.027]	0.952 [0.848-1.068]
Medicaid	0.72 [0.644-0.805]	0.977 [0.836-1.143]
Other/unknown	0.787 [0.708- 0.875]	0.908 [0.784-1.05]
Median Income		
Bottom quartile/unknown	Ref	Ref
Second quartile	1.025 [0.943-1.114]	0.957 [0.847- 1.081]
Third quartile	1.084 [0.995-1.18]	0.958 [0.847-1.081]
Fourth quartile	1.09 [0.995-1.193]	1.036 [0.909-1.18]
Year of Diagnosis		
2004	1.139 [0.996-1.302]	1.205 [0.986-1.473]
2005	0.962 [0.848-1.091]	0.992 [0.825-1.192]
2006	1.242 [1.099-1.403]	1.213 [1.018-1.445]
2007	1.143 [1.017-1.284]	1.147 [0.973-1.352]
2008	1.005 [0.901-1.122]	1.029 [0.881-1.201]
2009	1.009 [0.907-1.122]	1.108 [0.951-1.29]
2010	0.856 [0.771-0.95]	0.907 [0.783-1.05]
2011	0.994 [0.896-1.103]	1.044 [0.903-1.208]
2012	0.882 [0.796-0.977]	0.905 [0.786-1.042]
2013	Ref	Ref
Charlson Score		
0	0.835 [0.724-0.962]	0.831 [0.667-1.036]
1	0.873 [0.75- 1.015]	0.841 [0.666-1.063]
2	Ref	Ref
Clinical T stage		
T1	0.2 [0.146-0.274]	0.689 [0.502-0.947]
T2	0.277 [0.236-0.325]	1.003 [0.832- 1.209]
T3	0.405 [0.364-0.450]	0.947 [0.822-1.092]

T4	Ref	Ref
Clinical N stage		
N0	1.71 [1.534-1.907]	-
N1	1.37 [1.231-1.525]	1.799 [1.612-2.008]
N2	Ref	Ref
Histologic Grade		
Well differentiated	0.719 [0.635-0.813]	0.833 [0.692-1.002]
Moderate differentiated	0.632 [0.582-0.685]	0.789 [0.7-0.89]
Poorly differentiated	0.392 [0.352-0.437]	0.404 [0.347-0.47]
Undifferentiated	0.302 [0.229-0.397]	0.466 [0.326-0.666]
Unknown	Ref	Ref
Radiation Dose (cGy)		
<=4500	0.987 [0.885-1.1]	1.098 [0.939-1.283]
4501 – 5039	1.091 [0.994-1.197]	1.252 [1.097-1.429]
>= 5040	1.024 [0.912-1.149]	1.043 [0.886-1.229]
Unknown	Ref	Ref
Lymph Nodes Examined		
1-5	1.331 [1.209-1.466]	1.844 [1.566-2.173]
6-10	Ref	Ref
11-15	0.859 [0.799-0.925]	0.891 [0.799-0.993]
16-20	0.818 [0.753-0.888]	0.815 [0.723-0.918]
20+	0.763 [0.699-0.833]	0.784 [0.693-0.888]
Time between radiation and surgery (days)	1 [0.999–1.002]	1.002 [1- 1.004]

Abbreviations: ref = reference.

Supplemental Table 2. The following table represents the results of the full multivariable Cox regression model to identify predictors of overall survival. We constructed two separate models, the first model (left column) included the interaction with complete primary tumor response (pT0/pTis/pTx) and age, and the second model (right column) included the interaction with complete lymph node response (pN0/pNx) and age. The analysis of primary tumor complete response included the whole study cohort, and the analysis of lymph node complete response included only those with nodal involvement at diagnosis.

	Hazard ratio for overall survival [95% confidence interval]	
Characteristic	**Primary tumor response**	**Lymph node response**
Age (years)		
18-39	0.564 [0.478-0.666]	0.658 [0.516-0.839]
40-49	0.52 [0.463-0.585]	0.655 [0.543-0.791]
50-59	0.578 [0.522-0.639]	0.701 [0.593-0.828]
60-69	0.667 [0.614-0.725]	0.792 [0.683-0.919]
70+	Ref	Ref
Complete pathologic response		
18-39	0.413 [0.278-0.615]	0.315 [0.221-0.45]
40-49	0.51 [0.412-0.631]	0.382 [0.312-0.467]
50-59	0.618 [0.54-0.707]	0.462 [0.401-0.533]
60-69	0.707 [0.628-0.797]	0.459 [0.399-0.527]
70+	0.737 [0.66-0.823]	0.617 [0.536-0.71]
Sex		
Male	1.205 [1.14-1.273]	1.194 [1.107-1.288]
Female	Ref	Ref
Race		
White	Ref	Ref
Black	1.124 [1.022-1.235]	1.109 [0.975-1.261]
Unknown	0.98 [0.864-1.112]	0.982 [0.827-1.167]
Ethnicity		
Non-Hispanic	0.933 [0.849-1.025]	0.894 [0.784-1.02]
Hispanic	0.704 [0.597-0.829]	0.652 [0.521-0.816]
Other	Ref	Ref
Insurance		
Private	Ref	Ref
Medicare	1.274 [1.136-1.428]	1.31 [1.123-1.528]
Medicaid	1.251 [1.158-1.352]	1.292 [1.159-1.441]
Other/unknown	1.367 [1.233-1.516]	1.317 [1.149-1.51]
Median Income		
Bottom quartile/unknown	Ref	Ref
Second quartile	0.9 [0.834-0.973]	0.891 [0.799-0.992]
Third quartile	0.827 [0.766-0.894]	0.786 [0.706-0.876]
Fourth quartile	0.689 [0.636-0.746]	0.691 [0.618-0.772]
Year of Diagnosis		
2004	0.985 [0.846-1.145]	1.036 [0.843-1.273]
2005	0.953 [0.822-1.106]	0.964 [0.788-1.179]
2006	0.993 [0.858-1.15]	0.944 [0.775-1.151]
2007	0.973 [0.841-1.125]	0.962 [0.792-1.168]
2008	0.949 [0.822-1.095]	0.942 [0.777-1.141]
2009	1.089 [0.945-1.254]	1.183 [0.979-1.429]
2010	0.989 [0.855-1.143]	0.959 [0.789-1.166]
2011	0.975 [0.838-1.134]	0.973 [0.795-1.192]
2012	Ref	Ref
Charlson Score		
0	0.512 [0.456-0.574]	0.563 [0.474-0.668]
1	0.641 [0.565-0.726]	0.717 [0.596-0.863]
2+	Ref	Ref
Clinical T stage		

T1	0.498 [0.355-0.698]	0.471 [0.333-0.667]
T2	0.492 [0.419-0.578]	0.5 [0.418-0.599]
T3	0.626 [0.575-0.682]	0.673 [0.595-0.761]
T4	Ref	Ref
Clinical N stage		
N0	0.633 [0.571-0.702]	-
N1	0.739 [0.667-0.82]	0.827 [0.745-0.918]
N2	Ref	Ref
Histologic Grade		
Well differentiated	0.994 [0.873-1.13]	1.068 [0.891-1.28]
Moderate differentiated	1.037 [0.951-1.129]	1.065 [0.944-1.2]
Poorly differentiated	1.744 [1.576-1.93]	1.594 [1.388-1.832]
Undifferentiated	2.181 [1.737-2.739]	2.199 [1.645-2.941]
Unknown	Ref	Ref
Radiation Dose (cGy)		
<=4500	1.112 [1.008-1.228]	1.168 [1.019-1.34]
4501 – 5039	1.016 [0.931-1.11]	1.071 [0.948-1.21]
>= 5040	1.058 [0.951-1.176]	1.03 [0.888-1.194]
Unknown	Ref	Ref
Lymph Nodes Examined		
1-5	1.083 [0.996-1.178]	1.118 [0.985-1.27]
6-10	Ref	Ref
11-15	0.915 [0.851-0.983]	0.883 [0.799-0.976]
16-20	0.89 [0.818-0.968]	0.904 [0.807-1.014]
20+	0.893 [0.817-0.976]	0.847 [0.752-0.955]
Time between radiation and surgery (days)	1.003 [1.002-1.004]	1.004 [1.002-1.005]

Abbreviations: ref = reference.

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