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Can We Eliminate Neoadjuvant Chemoradiotherapy in favor of Neoadjuvant Multi-Agent Chemotherapy for select Stage II/III Rectal Adenocarcinomas: Analysis of the National Cancer Database

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Abstract

BACKGROUND—Stage II and III rectal cancers have been effectively treated with neoadjuvant chemoradiotherapy (NCRT) followed by definitive resection. Advancements in surgical technique and systemic therapy have prompted investigation of neoadjuvant multi-agent chemotherapy (NMAC) regimens with the elimination of radiation (RT). The purpose of our study was to investigate factors predicting for the use of NCRT versus NMAC and compare outcomes using the National Cancer Data Base (NCDB) for select Stage II/III rectal cancers.

METHODS—In the NCDB, 21,707 patients from 2004-2012 with clinical T2N1, T3N0, or T3N1 rectal cancers were identified treated with NCRT or NMAC followed by low anterior resection (LAR). Kaplan-Meier method, log-rank test, and Cox-proportional hazard regression analyses were conducted along with propensity-score-matching (PSM) analysis to reduce treatment selection bias.

RESULTS—5-year actuarial overall survival (OS) was 75.0% for patients receiving NCRT versus 67.2% for patients receiving NMAC ($p < 0.01$). On MVA, NCRT patients had improved OS ($HR = 0.77$, $p < 0.01$); this effect was confirmed on PSM analysis ($HR = 0.72$, $p = 0.01$). In the same

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model, age <65 years old, having private insurance, treatment at an academic center, living in an affluent zip code, low co-morbidity score, receipt of adjuvant chemotherapy, and shorter duration to surgery had improved OS (all $p<0.05$). African-American race, male gender, high grade tumors, cT3N1 tumors, and R1 resections had worse OS (all $p<0.05$).

CONCLUSIONS—In this series, elimination of neoadjuvant RT for select Stage II/III rectal adenocarcinoma was associated with worse OS and should not be recommended outside of a clinical trial.

Keywords

Rectal cancer; neoadjuvant chemoradiation; neoadjuvant chemotherapy; National Cancer Database (NCDB); health disparities

INTRODUCTION

An estimated 40,000 new cases of rectal cancer are diagnosed in the United States annually¹. Since 1990, the standard of care for Stage II (T3 and T4 tumors as defined by the AJCC staging system²) and Stage III (N1 or N2 disease as defined by the AJCC staging system²) is tri-modality therapy of radiation, chemotherapy, and surgery³. Historical studies showed that pelvic radiation (RT) reduced local rectal cancer recurrence and increased the chance for sphincter preservation with surgery⁴⁻⁶. The sequencing of chemoradiotherapy (CRT) for Stage II and III tumors was defined based on a landmark German randomized trial showing that neoadjuvant CRT had reduced local recurrence, improved sphincter preservation, and improved side effect profile^{7, 8}. These results were confirmed in the United States with NSABP R-03⁹, and as a result the standard of care for locally advanced rectal cancers is preoperative CRT with 5-FU followed by surgical resection and additional adjuvant chemotherapy.

Recently, with the incorporation of total mesorectal excision (TME) surgical principles^{10, 11} and improved systemic therapy^{12, 13}, the benefit of pelvic radiation is being challenged. CRT is associated with short term toxicity in 50% of patients as well as long term effects including fibrosis, fecal incontinence, bladder and sexual dysfunction, and myelosuppression¹⁴⁻¹⁷. From a chemotherapy perspective, less toxicity has been reported with preoperative chemotherapy versus postoperative¹⁸. This rationale prompted investigational use of neoadjuvant multi-agent chemotherapy (NMAC) followed by excision, eliminating pelvic radiation, with a pilot trial showing promising results¹⁹. The accruing PROSPECT Trial is implementing this paradigm nationally for clinically staged T3N0, T3N1, and T2N1 rectal cancer²⁰. Given the small number of patients studied with this evolving regimen, we used the National Cancer Data Base (NCDB) to identify patients who appear to meet eligibility criteria for the PROSPECT trial to determine the impact of NMAC versus neoadjuvant chemoradiotherapy (NCRT) on overall survival (OS), as well as determine variables that predicted for patients receiving NMAC versus NCRT.

METHODS

NCDB Criteria

The NCDB is a large, prospectively acquired database, drawn from cases from Commission on Cancer (CoC) accredited institutions across the United States, capturing approximately 70% of all newly diagnosed malignancies in the United States. The dataset includes detailed information on patient, disease, and treatment characteristics as well as survival outcomes. This database includes detailed radiotherapy (RT) information regarding treatment site, radiation source and dose, as well as detailed surgical and pathological information including type of surgery, margin status, and number of lymph nodes removed.

The rectal NCDB was queried for patients over the age of 18 diagnosed from 2004 to 2012. Patients with clinically staged T2N1, T3N0, and T3N1 rectal adenocarcinomas treated with NCRT or NMAC followed by a low anterior resection (LAR) were included. Patients treated with abdominoperineal resection, did not receive neoadjuvant therapy, treated with nonmegavoltage photon beam radiation, received single agent chemotherapy alone and patients who had medical reasons to not receive radiation or lack of survival information were excluded (**Figure 1**). The following patient characteristics were examined: age (<65, 65 years old), race (white, African-American, other), sex, treatment facility type (community cancer center, comprehensive community cancer center, or academic/research program), treatment facility geographical region, insurance coverage (not insured, private insurance, government insurance [including Medicaid and VA], and Medicare insurance), patient county of residence (urban, rural, or metro), distance from patient residence zip code to treatment facility (<10 miles, 10-50 miles, or >50 miles), year of diagnosis (2004-2006, 2007-2009, and 2010-2012), patient education and income based on county of residence (determined by 2012 American Community Survey administered by the U.S. Census), and co-morbidities as quantified by the Charlson-Deyo score^{21, 22}. The following disease characteristics were evaluated: tumor grade (low, moderately, or poorly differentiated), lymphovascular invasion, serum carcinoembryonic antigen (positive or negative as defined by values above the upper limit of normal), tumor stage, pathological downstaging (complete response defined as ypT0N0, partial response defined as any T or N regression, and no response), and tumor regression grade (based on pathological assessment, ranging from complete response [no viable cancer cells] to poor response [extensive residual cancer cells]). Finally, the following treatment characteristics were also evaluated: receipt of NMAC or NCRT, time from end of neoadjuvant therapy to surgery (<1 month, 1-3 months, and >3 months), extent of resection (R0 or R1), number of lymph nodes surgically examined (0-7, 8-12, 12-17, and 18), and use of adjuvant chemotherapy (yes or no).

Statistical Methods

Statistical analysis was conducted using SAS Version 9.4, and SAS macros developed by Biostatistics and Bioinformatics Shared Resource at Winship Cancer Institute²³. Descriptive statistics for each variable were determined. Follow up was determined by the reverse Kaplan-Meier method²⁴. The univariate association of each covariate with receipt of NCRT versus NMAC was assessed using the Chi-square test for categorical covariates and ANOVA for numerical covariates. The primary endpoint of OS was defined as months from LAR to

death from any cause or last follow up if alive. The univariate association (UVA) of each variable with OS was tested by Cox proportional hazards models and log-rank tests. A multivariable Cox proportional hazard model (MVA) was fit by a backward elimination method applying $p = 0.20$ removal criteria. The effect of CRT vs. NAMC on OS stratified by different variables was estimated by testing the interaction effect between each modality and each relevant variable. Of note, lymphovascular space invasion, serum carcinoembryonic antigen, and tumor regression grade were eliminated from MVA due to the high number of patients missing this data. Kaplan-Meier plots were produced to compare the survival curves by subgroups along with log-rank p -value, and <0.05 was considered statistically significant.

Propensity score matching (PSM) method was then conducted to address a potential treatment selection bias. A logistic regression model predicting use of CRT versus NAMC was carried out to predict the propensity score by age, race, facility type and location, insurance status, county of residence, distance to treatment facility from home zip code, year of diagnosis, education and income level of home zip code, Charlson-Deyo score, lymph node positivity, T2N1 vs. T3N0 vs. T3N1 tumors, tumor grade, surgical margin, number of regional nodes examined, time from start of neoadjuvant therapy to surgery, and use of adjuvant chemotherapy. Patients from NAMC were matched to NCRT patients at a ratio of 1:5 based on the propensity score using a greedy algorithm and using a SAS macro provided by the Mayo Clinic²⁵. The matching caliper was set at 0.2 standard deviation of logit of the propensity score. After matching, the balance of covariate between two cohorts was evaluated by the standardized differences and a value of < 0.1 was considered as negligible imbalance²⁶. The effects were estimated in the matched sample by a Cox model with a robust variance estimator²⁷ for OS.

RESULTS

Patient Characteristics

A total of 21,707 patients met study entry criteria (see **Figure 1**); of these 274 (1.3%) were treated with NAMC. The median age at diagnosis was 60 years (range 18-90 years old). Overall, the median follow-up was 123.3 months. The median distance from a patient's zip code to treatment facility was 11.2 miles. The median time from the end of neoadjuvant therapy to low anterior resection was 62 days. For patients in the NCRT group, the median dose of RT was 50.4 Gy (range 45 to 60 Gy). The median daily dose of RT was 1.8 Gy. **Table 1** summarizes the study population.

Predictors of Receipt of Neoadjuvant Treatment Type

On UVA, age less than 65 years, northeast and midwest practice locations, having government insurance or lack of insurance, patient's zip code within 50 miles of treatment facility and treatment at community based programs were demographic factors predictive of receiving NCRT. Node positive tumors (T2N1 or T3N1), having a complete pathological response, and time from the end of neoadjuvant therapy to surgery of 1-3 months were tumor and treatment factors associated with receipt of NCRT versus NAMC (all $p < 0.05$; see Supplemental Table 1). On MVA, distance from home zip code to treatment facility of less

than 50 miles, lack of insurance, and T3N1 tumors, were all more likely to receive NCRT versus NMAC (all $p < 0.01$; see **Table 2**).

Impact of Neoadjuvant Treatment Type on Overall Survival

The actuarial 5-year OS was 75.0% for patients treated with NCRT compared with 67.2% for patients treated with NMAC ($p < 0.01$; see **Figure 2**). NCRT was associated with improved OS on UVA (HR=0.74, 95% CI 0.58-0.93; $p < 0.01$; see Supplemental Table 2) and MVA (HR=0.77, 95% CI 0.61-0.97; $p = 0.03$). On MVA, additional variables associated with improved OS included age < 65 years old, treatment at an academic cancer program, having private insurance, living in a zip code with median income greater than \$46,000, Charlson-Deyo score of 0 or 1, having at least 12 lymph nodes examined during surgery, and LAR within 1-3 months from the end of neoadjuvant therapy (all $p < 0.05$; see Table 3). Additional variables associated with worse OS on MVA included African-American race, male gender, diagnosis between 2010-2012, poorly differentiated tumors, cT3N1 tumors, R1 resections, and patients not receiving adjuvant chemotherapy (all $p < 0.05$; see **Table 3**). Use of NCRT did not have significant interaction effect with tumor stage, facility type, and time from end of neoadjuvant therapy to surgery on overall survival (all $p > 0.10$) indicating a benefit to NCRT across all levels of these variables.

Impact of Neoadjuvant Therapy on Overall Survival with Propensity Score Matching Analysis

After matching, PSM analysis identified 1,343 patients receiving NCRT and 274 patients receiving NMAC, with the two groups being balanced in demographic, tumor, and treatment characteristics (see Supplemental Table 3). On PSM, the 5-year actuarial overall survival was 73.4 % in patients receiving NCRT compared with 65.8% in patients receiving NMAC ($p = 0.02$; **Figure 3**). Cox analysis of the PSM patient cohorts, there was statistically significant improved OS with NCRT (HR=0.72, 95% CI 0.56-0.93; $p = 0.01$).

DISCUSSION

In this analysis of the NCDB, we found that use of NCRT in patients with clinical T2N1, T3N0, and T3N1 rectal adenocarcinomas treated with LAR, is associated with improved OS compared with NMAC on UVA, MVA, and interaction effect testing. This survival benefit persisted when propensity score matching was implemented to balance the two cohorts for patient, tumor, and treatment characteristics. Our study is the first in the literature to compare these two neoadjuvant treatment strategies head-to-head as well as to examine factors predicting for treatment choice. We found that patient's living in a zip code within 50 miles of treatment facility, lack of insurance, and T3N1 tumors were more likely to receive NCRT. Our study also confirmed known poor prognostic factors in rectal cancer including inadequate lymph node dissection, delay to surgery after neoadjuvant therapy²⁸, incomplete resection, poorly differentiated tumors, and higher stage tumors.

There is a movement to eliminate or reduce the use of NCRT in favor of NMAC in select patients, as evidenced by the ongoing PROSPECT Trial, to decrease RT induced toxicity^{14-17, 29}. The basis of this accruing trial is from a pilot single-arm phase II study

from Memorial Sloan-Kettering Cancer Center that enrolled 32 patients¹⁹. These patients were clinically staged as T3 (N0 or N1) with MRI and endoscopic rectal ultrasound (ERUS), deemed resectable, and did not require temporary diverting ostomy or endorectal stent. Each patient received four cycles of mFOLFOX6³⁰ with bevacizumab followed by two cycles of mFOLFOX alone. If there was any progression, patients instead received concurrent 5FU and RT. Surgery with TME was performed 3 to 6 weeks from completion of neoadjuvant therapy. Adjuvant chemotherapy was personalized, with FOLFOX being recommended by the investigators. All patients had an R0 resection, with 25% having a pathological complete response. Only two patients required neoadjuvant radiation due to FOLFOX intolerance, with one requiring adjuvant radiation. The 4 year results were extremely promising, showing 0% local recurrence and 91% overall survival¹⁹, prompting the creation of the PROSPECT Trial. The PROSPECT trial randomizes cT2N1, cT3N0, and cT3N1 rectal adenocarcinomas to 6 cycles of FOLFOX versus the standard concurrent 5FU and RT to 50.4 Gy. Patients are clinically and radiographically (via MRI or ERUS) assessed in the FOLFOX group and if there is no progression and estimated regression of $\geq 20\%$ they proceed to LAR with TME. Patients who progress or do have $<20\%$ regression received standard concurrent 5FU and RT. Systemic chemotherapy is delivered after surgery, with adjuvant CRT recommended for patients who do not achieve an R0 resection and did not receive radiation preoperatively. This trial is currently enrolling patients at multiple sites in the United States²⁰.

There are several reasons for the interest in elimination of NCRT from the treatment paradigm in rectal cancer. Justification for the elimination of upfront radiation therapy in all Stage II and III rectal cancers patients comes from low local recurrence rates observed with modern TME techniques, with overall 5-year estimates of less than 10%^{10, 11, 31}. Moreover, randomized evidence shows RT improves local control in the TME era with no improvement in OS³². Improved systemic therapies^{12, 13, 33}, with increasing cases of pathological complete response and longer disease free survival intervals, have also been used to rationalize the elimination of radiation. However, beyond the above mentioned single arm study of 32 patients, there is lack of prospective evidence to eliminating radiation in Stage II/III rectal cancers. There is a recently published Canadian review examining 566 patients who would meet eligibility for the PROSPECT trial which found that these patients had improved recurrence free survival (HR=0.75) compared to patients who did not meet enrollment criteria, suggesting that elimination of radiation could be considered²⁹.

Our study has several strengths and limitations. The strengths include that our series serves as the largest assessment of the use of NMAC in cT2N1, cT3N0, and cT3N1 patients, and serves as the only comparison of these patients to the current standard of care of NCRT. Additionally, we are the first to summarize these practice patterns in the United States as well as report on factors that potentially influence clinician treatment modality choice. The limitations of our study are the lack of uncaptured variables by the NCDB, like other cancer registries, leading to a potential inherent imbalance between the NCRT and NMAC group. We performed stratified analysis, PSM, and interaction variable testing to account for these confounding variables, and there was a persistent OS benefit to NCRT, but even with these multiple statistical methods to balance the cohorts there may be confounders that cannot be accounted for in the NCDB. We excluded patients who were coded as not being able to receive radiation due to medical reasons, but there may be confounding uncaptured reasons

why a patient did not get radiation that could impact OS. Additionally, we cannot determine specifically if all of the patients in the NMAC would meet eligibility criteria for the PROSPECT Trial. We can infer they are a similar cohort based on clinical stage, surgery modality, and their OS outcomes, but we do not have specific information on methods used to stage these patients or information on clinical response prior to surgery. Additionally, we cannot capture specific chemotherapy regimens in the NCDB, and can only assess that patients had multi-agent chemotherapy in the NMAC group and single-agent chemotherapy in the NCRT group. Toxicity information and patient reported outcomes are not reported, so we cannot comment on the morbidity of the treatment regimens. Lastly, the NCDB does not provide information on cause of death, and it is possible that the OS benefit to NCRT on stratified analysis is due to competing risks of death.

CONCLUSION

In summary, our series indicates that the use of NCRT is associated with improved OS compared with NMAC on stratified analysis for select Stage II/III rectal adenocarcinomas treated with LAR. This benefit persisted when demographic, tumor, and treatment variables are balanced. Patients that lived in a zip code within 50 miles of their treatment facility, had more advanced disease, and lacked insurance were more likely to receive NCRT over NMAC. Until the results of the accruing PROSPECT trial are published, our series suggests that cT2N1, cT3N0, and cT3N1 rectal adenocarcinomas should receive NCRT, with NMAC reserved for clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
CONSORT diagram of the study population.

Treatment	No. of Subject	1 Year Overall Survival (95% CI)	5 Year Overall Survival (95% CI)
NMAC	274	92.1% (88.2%, 94.8%)	67.2% (59.5%, 73.8%)
NCRT	21432	95.5% (95.2%, 95.8%)	75.0% (74.3%, 75.7%)

Figure 2.
Overall survival amongst patients treated with neoadjuvant chemoradiotherapy (NCRT) compared with patients treated with neoadjuvant multi-agent chemotherapy (NMAC).

Treatment	Number of Patients	1 Year Overall Survival	5 Year Overall Survival
NCRT	1133	94.7% (93.2%, 95.8%)	73.4% (69.9%, 76.7%)
NMAC	233	92.0% (87.6%, 94.9%)	65.8% (56.8%, 73.4%)

Figure 3. Overall survival on propensity score matched analysis comparing patients receiving neoadjuvant chemoradiotherapy (NCRT) to patients receiving neoadjuvant multi-agent chemotherapy (NMAC).

Table 1

Summary of patient demographic, socioeconomic, tumor, and treatment characteristics.

Variable	N = 21,707 (%)
<i>Patient Characteristics</i>	
Age at Diagnosis (Years)	
<65	13,508 (62.2)
65	8,199 (37.8)
Sex	
Male	13,616 (62.7)
Female	8,091 (37.3)
Race	
White	18,932 (87.2)
African American	1,669 (7.7)
Other/Missing	1,106 (5.1)
Facility Type	
Community Cancer Program	3,728 (17.2)
Comprehensive Community Cancer Program	9,583 (44.1)
Academic/Research Program	7,452 (34.3)
Unknown	944 (4.3)
Facility Location	
Northeast	3,996 (18.4)
South	7,234 (33.3)
Midwest	6,582 (30.3)
West	2,951 (13.6)
Unknown	944 (4.3)
Distance from Home Zip Code to Treatment Facility	
<10 Miles	9,871 (46.0)
10-50 Miles	8,954 (41.7)
>50 Miles	2,638 (12.3)
Missing	244
Insurance Status	
Not Insured	959 (4.4)
Private Insurance	11,250 (51.8)
Government Insurance (Medicaid & VA)	1,464 (6.7)
Medicare	7,618 (35.1)
Missing	416 (1.9)
County of Residence	
Rural	527 (2.4)

Variable	N = 21,707 (%)
Urban	3,958 (18.2)
Metro	16,617 (76.6)
Missing	605 (2.8)
Median Income Quartile of County of Residence	
<\$30,000	2,605 (12.0)
\$30,000 - \$35,999	3,994 (18.4)
\$36,000 - \$45,999	6,018 (27.7)
\$46,000+	8,335 (38.4)
Missing	755 (3.5)
Percent No High School Degree in Patient County of Residence	
29%	3,275 (15.1)
20-28.9%	4,912 (22.6)
14-19.9%	5,328 (24.5)
<14%	7,435 (34.3)
Missing	757 (3.5)
Year of Diagnosis	
2004-2006	5,299 (24.4)
2007-2009	7,247 (33.4)
2010-2012	9,161 (42.2)
Charlson-Deyo Score	
0	17,480 (80.5)
1	3,432 (15.8)
2+	795 (3.7)
<i>Tumor Characteristics</i>	
Stage	
T2N1	1,056 (4.9)
T3N0	11,366 (52.4)
T3N1	9,285 (42.8)
Grade	
Well Differentiated	1,522 (7.0)
Moderately Differentiated	14,969 (69.0)
Poorly Differentiated	2,265 (10.4)
Not Determined/Missing	2,951 (13.6)
Lymphovascular Invasion	
Yes	891 (4.1)
No	6,059 (86.8)
Missing	14,726
Carcinoembryonic Antigen	

Variable	N = 21,707 (%)
Positive	5,517 (40.9)
Negative	7,985 (59.1)
Missing	8,205
<i>Treatment Characteristics</i>	
Type of Neoadjuvant Therapy	
Multi-agent Chemotherapy (NMAC)	274 (1.3)
Concurrent Chemoradiotherapy (NCRT)	21,433 (98.7)
Tumor Regression Grade Based on Pathological Response	
Complete Response (no viable cancer cells)	1,793 (52.8)
Moderate Response (single cells or small groups)	1,051 (31.0)
Minimal Response (residual cancer)	550 (16.2)
Poor Response (extensive residual cancer)	43
Missing	16,866
Pathological Downstaging	
Complete (ypT0N0)	2,236 (13.2)
Partial Response	6,176 (36.5)
No Response	8,517 (50.3)
Missing	4,778
Number of Regional Lymph Nodes Examined	
0-7	6,063 (28.7)
8-11	5,238 (24.8)
12-17	5,224 (24.7)
17+	4,617 (21.8)
Missing	565
Extent of Resection	
R0	20,061 (92.4)
R1	891 (4.1)
Missing	755 (3.5)
Time from End of Neoadjuvant Therapy to Surgery	
<1 month	226 (1.0)
1-3 months	10,512 (48.4)
3-6 months	10,969 (50.5)
Adjuvant Chemotherapy	
Yes	6,047 (33.0)
No	12,251 (67.0)
Missing	3,409

Table 2

Multivariable Analysis^{*} of factors predicting for the use of neoadjuvant chemoradiotherapy (NCRT) over neoadjuvant multi-agent chemotherapy (NMAC).

Variable	Odds Ratio (95% CI)	OR P-value	P-value
Patient Characteristics			
Insurance Status			
Unknown	0.29 (0.11-0.80)	0.02	<0.01
Medicare	0.46 (0.21-1.00)	0.05	
Government Insurance (Medicaid & VA)	0.60 (0.25-1.44)	0.25	
Private Insurance	0.68 (0.32-1.47)	0.33	
Not Insured	--	--	
Distance from Home Zip Code to Treatment Facility			
<10 Miles	2.44 (1.65-3.60)	<0.01	<0.01
10-50 Miles	1.65 (1.16-2.36)	0.01	
>50 Miles	--	--	
Facility Location			
Unknown	1.11 (0.53-2.30)	0.79	0.06
West	0.68 (0.45-1.03)	0.07	
Midwest	1.17 (0.80-1.73)	0.42	
South	0.85 (0.60-1.23)	0.40	
Northeast	--	--	
County of Residence			
Unknown	1.04 (0.43-2.56)	0.93	0.11
Rural	2.07 (0.83-5.17)	0.12	
Urban	1.46 (1.03-2.07)	0.04	
Metro	--	--	
Tumor Characteristics			
Grade			
Well Differentiated	0.74 (0.45-1.21)	0.23	0.15
Moderately Differentiated	1.17 (0.83-1.66)	0.37	
Poorly Differentiated	1.20 (0.72-1.97)	0.49	
Not Determined/Missing	--	--	
Stage			
T2N1	1.21 (0.61-2.40)	0.59	0.01
T3N0	0.70 (0.54-0.90)	0.01	
T3N1	--	--	
Treatment Characteristics			
Number of Regional Lymph Nodes Examined			
0-7	0.80 (0.35-1.87)	0.61	

Variable	Odds Ratio (95% CI)	OR P-value	P-value
8-12	0.90 (0.38-2.10)	0.80	0.15
12-17	0.72 (0.31-1.68)	0.46	
17+	0.56 (0.14-1.29)	0.18	
Missing	--	--	
Time from End of Neoadjuvant Therapy to Surgery			
<1 month	1.21 (0.61-2.40)	0.59	0.01
1-3 months	0.70 (0.54-0.90)	0.01	
3-6 months	--	--	

* Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: Age at diagnosis, Charlson-Deyo Score, facility type, median income of county of residence, percent of county of residence without high school degree, race, surgical margins, sex, use of adjuvant chemotherapy, and year of diagnosis.

Table 3

Multivariable Analysis^{*} of patient, tumor, and treatment factors and their association with overall survival.

Variable	Hazard Ratio (HR) (95% CI)	HR P-value	P-value
<i>Patient Characteristics</i>			
Age at Diagnosis (Years)			
65	1.54 (1.38-1.71)	<0.01	<0.01
<65	--	--	
Facility Type			
Comprehensive Community Cancer Program	1.02 (0.93-1.11)	0.74	<0.01
Academic/Research Program	0.85 (0.77-0.94)	0.01	
Unknown	0.74 (0.60-0.93)	0.01	
Community Cancer Program	--	--	
Race			
Other/Missing	0.93 (0.78-1.10)	0.38	0.01
African American	1.22 (1.08-1.37)	0.01	
White	--	--	
Sex			
Male	1.22 (1.14-1.31)	<0.01	<0.01
Female	--	--	
Insurance Status			
Missing/Unknown	0.77 (0.54-1.11)	0.16	<0.01
Private Insurance	0.71 (0.60-0.84)	<0.01	
Government Insurance (Medicaid & VA)	0.98 (0.80-1.20)	0.83	
Medicare	0.98 (0.81-1.18)	0.83	
Not Insured	--	--	
Median Income Quartile of County of Residence			
Missing/Unknown	1.37 (1.13-1.64)	<0.01	<0.01
<\$30,000	1.32 (1.18-1.47)	<0.01	
\$30,000 - \$35,999	1.17 (1.06-1.28)	<0.01	
\$36,000 - \$45,999	1.25 (1.15-1.35)	<0.01	
\$46,000+	--	--	
Charlson-Deyo Score			
0	0.50 (0.44-0.57)	<0.01	<0.01
1	0.65 (0.57-0.75)	<0.01	
2+	--	--	
Year of Diagnosis			
2004-2006	0.87 (0.77-0.97)	0.01	0.01
2007-2009	0.89 (0.82-0.96)	<0.01	

Variable	Hazard Ratio (HR) (95% CI)	HR P-value	P-value
2010-2012	--	--	
County of Residence			
Missing/Unknown	1.20 (1.01-1.43)	0.04	0.11
Rural	0.90 (0.75-1.09)	0.28	
Urban	0.97 (0.89-1.05)	0.40	
Metro	--	--	
<i>Tumor Characteristics</i>			
Grade			
Well Differentiated	1.15 (0.99-1.35)	0.07	<0.01
Moderately Differentiated	1.11 (1.00-1.23)	0.06	
Poorly Differentiated	1.70 (1.49-1.94)	<0.01	
Not Determined/Missing			
Stage			
T2N1	0.76 (0.63-0.91)	<0.01	<0.01
T3N0	0.88 (0.83-0.95)	<0.01	
T3N1	--		
<i>Treatment Characteristics</i>			
Type of Neoadjuvant Therapy			
Concurrent Chemoradiotherapy (NCRT)	0.72 (0.56-0.93)	0.01	0.01
Multi-agent Chemotherapy (NMAC)	--	--	
Surgical Margin			
Missing/Unknown	1.04 (0.85-1.28)	0.68	<0.01
Positive	2.53 (2.24-2.85)	<0.01	
Negative	--	--	
Number of Regional Lymph Nodes Examined			
Missing/Unknown	0.84 (0.70-1.02)	0.08	0.01
17+	0.89 (0.82-0.97)	0.01	
12-17	0.87 (0.81-0.95)	<0.01	
8-12	0.94 (0.87-1.01)	0.09	
0-7	--	--	
<i>Time to Surgery</i>			
Time from End of Neoadjuvant Therapy to Surgery			
<1 month	0.50 (0.32-0.79)	0.01	<0.01
1-3 months	0.86 (0.81-0.92)	<0.01	
3-6 months	--	--	
Adjuvant Chemotherapy			
No	1.38 (1.28-1.49)	<0.01	<0.01
Yes	--	--	

* Backward selection with an alpha level of removal of .2 was used. The following variables were removed from the model: distance from patient zip code to treatment facility, facility location, and percent of zip code without a high school degree in patient's county of residence.