Predictors of Guideline Treatment Nonadherence and the Impact on Survival in Patients With Colorectal Cancer

Robert B. Hines, PhD; Alina Barrett, MD; Philip Twumasi-Ankrah, PhD; Dominique Broccoli, PhD; Kimberly K. Engelman, PhD; Joaquina Baranda, MD; Elizabeth A. Ablah, PhD; Lisette Jacobson, PhD; Michelle Redmond, PhD; Wei Tu, PhD; and Tracie C. Collins, MD, MPH

Abstract

Background: This study investigated the effect of comorbidity, age, health insurance payer status, and race on the risk of patient nonadherence to NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon and Rectal Cancers. In addition, the prognostic impact of NCCN treatment nonadherence on overall survival was assessed. Patients and Methods: Patients with CRC who received primary treatment at Memorial University Medical Center from 2003 to 2010 were eligible for this study. Modified Poisson regression was used to obtain risk ratios for the outcome of nonadherence with NCCN Guidelines. Hazard ratios (HRs) for the relative risk of death from all causes were obtained through Cox regression. Results: Guideline-adherent treatment was received by 82.7% of patients. Moderate/severe comorbidity, being uninsured, having rectal cancer, older age, and increasing tumor stage were associated with increased risks of receiving nonadherent treatment. Treatment nonadherence was associated with 3.6 times the risk of death (HR, 3.55; 95% CI, 2.16–5.85) in the first year after diagnosis and an 80% increased risk of death (HR, 1.80; 95% CI, 1.14–2.83) in years 2 to 5. The detrimental effect of nonadherence declined with increasing comorbidity and varied according to age. Conclusions: Although medically justifiable reasons exist for deviating from NCCN Guidelines when treating patients with colorectal cancer (CRC), those who received nonadherent treatment had much higher risks of death, especially in the first year after diagnosis. This study’s results highlight the importance of cancer health services research to drive quality improvement efforts in cancer care for patients with CRC. (J Natl Compr Canc Netw 2015;13:51–60)

Background

Among all cancers in the United States, colorectal cancer (CRC) ranks third in incidence and mortality for both men and women. The public health impact of CRC has improved over the past 3 decades, as evidenced by a declining incidence and mortality that is attributed to an increased use of screening modalities and improvements in treatment. Despite these encouraging trends, incongruity exists between what is considered the best possible cancer care and the actual care many patients receive.

NCCN developed treatment guidelines to assist providers involved in the management of patients with CRC. However, many patients do not receive guideline-adherent care, which results in a poorer prognosis. Increasing age is identified as a risk factor for not receiving neoadjuvant/adjuvant chemoradiation, despite the fact that older patients are shown to benefit from these treatments. Because increasing comorbidity is associated with advancing age, many physicians choose less aggressive treatment because of perceptions of an increased risk of treatment-related toxicity and poorer survival from competing causes of death. Balancing the optimal treatment for patients with CRC within the context of comorbidity burden and life expectancy is a major challenge to delivering high-quality cancer care.

In addition to age and comorbidity, race and socioeconomic status (SES) are associated with receipt of CRC treatment. Several investigators have documented a decreased likelihood of African American, Medicaid, and uninsured patients receiving treatment for CRC. Patients with lower SES also have a higher comorbidity burden that is likely related to lack of health care access, lower health literacy, higher preva-
lence of unhealthy behaviors, and the chronic strain of financial insecurity.28,29 The increased risk of death in patients of lower SES who have CRC may be from the combined effects of the aforementioned risk factors and a higher comorbidity burden, both of which are associated with a decreased likelihood of receiving treatment for CRC and worse prognosis.30

This study investigates the effect of comorbidity, age, health insurance payer status, and race on the risk of patient nonadherence with NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon/Rectal Cancer. It also assesses the effect of nonadherence to treatment guidelines and the aforementioned risk factors on overall survival after CRC diagnosis. The results of this study seek to identify patient characteristics that are associated with NCCN Guidelines nonadherence and quantify its prognostic impact on survival. Health services research on the quality of care that patients with CRC receive after diagnosis and the impact on survival is a vital component of quality improvement efforts in cancer care.

Methods

Study Population and Design
This was a retrospective cohort study of patients with CRC diagnosed between 2003 to 2010 who received primary cancer treatment at Memorial University Medical Center (MUMC) in Savannah, Georgia (N=852). The study termination date was September 30, 2011. The cancer registry at MUMC was the source of the study population. The final study population consisted of 677 patients, with 175 patients excluded based on the following exclusion criteria: stage 0 disease (n=82); missing/unknown disease stage (n=7); age older than 85 years (n=30); survival from diagnosis of less than 2 weeks (n=16); race other than black or white (n=9); stage II/III rectosigmoid cancer (n=29); and unknown insurance status (n=2). This research was approved by the Institutional Review Boards of Georgia Southern University and MUMC.

Study Variables
The cancer registry at MUMC is a Commission on Cancer–approved registry and collects demographic, comorbidity, tumor-related, treatment-related, and follow-up information on all patients treated at MUMC. The TNM system was used to classify tumors, and CRC staging (I–IV) was performed according to the AJCC system.31 Treatment was dichotomized as yes/no for surgery, chemotherapy, and radiation. Adherence with treatment guidelines was defined as concordance with a minimum set of recommendations from the NCCN stage-specific guidelines for CRC (Table 1).6,7 Patients were classified as nonadherent if they failed to receive one or more treatment modalities that constitute guideline-recommended treatment.

Comorbid diseases at the time of CRC diagnosis are recorded by registry staff. A maximum of 4 conditions could be entered for a patient, per registry protocol. From this information, the investigators used the method described by van Walraven et al32 to obtain a comorbidity score according to the Elixhauser comorbidity index.33 As has been demonstrated,32 patients were classified as having “no,” “mild,” “moderate,” or “severe” comorbidity. To ensure adequate numbers for analysis, the moderate and severe categories were combined.

Statistical Analysis
Descriptive statistics for categorical variables are presented as frequencies and percentages. Characteristics of study cases were compared according to adherence with NCCN treatment guidelines and differences in proportions tested by Chi-square sta-

| Table 1 Adherence* With NCCN Guidelines for Colon and Rectal Cancers |
|---------------------------------|-------------------------------------------------|
| Colon Cancer                    |                                                 |
| Stages I–II                     | Patients receive surgery with curative intent   |
| Stage III                       | Patients with AJCC stage III disease receive surgery followed by adjuvant chemotherapy |
| Stage IV                        | Systemic chemotherapy                           |
| Rectal Cancer                   |                                                 |
| Stage I                         | Patients receive surgery with curative intent   |
| Stages II–III                   | Patients with regional (AJCC stage II) or regional with lymph node involvement (AJCC stage III) receive surgery and both radiation and chemotherapy (neoadjuvant or adjuvant) |
| Stage IV                        | Systemic chemotherapy                           |

*Minimum treatment received to be defined as adherent.
tistics. The Kaplan-Meier method was used to estimate survivor functions and obtain the 25% death time with a 95% CI. Difference in survivor functions was tested by the log-rank test. All statistical tests were 2-sided. A P value less than .05 was considered statistically significant.

For the outcome of nonadherence with NCCN Guidelines, the modified Poisson regression approach described by Zou\textsuperscript{34} was used to calculate multivariable risk ratios (cumulative incidence ratios [CIRs]) with 95% CIs for the relative risk of nonadherence. Based on the bivariate relationship between risk factors/confounders with nonadherence, all variables associated with nonadherence at a P value of less than .20 were included in the initial model with comorbidity, age, health insurance payer status, and race. Manual backward elimination was used to arrive at the final model.

For the survival analysis, survival time was calculated from the date of first CRC diagnosis until either the date of death, last date of follow-up, or study termination date (September 30, 2011). No information was available on the specific causes of death; thus, the outcome was 5-year overall survival with death from any cause as the primary end point. The Cox proportional hazards model was used to obtain hazard ratios (HRs) with 95% CIs for the relative risk of death. The model-building procedure was the same as that described for the model of treatment nonadherence. The proportional hazards assumption was evaluated for guideline-based treatment, comorbidity, race, and payer status. Guideline-based treatment violated the proportional hazards assumption. Therefore, for guideline-based treatment only, the adjusted HRs were reported for the risk of death during the first year of follow-up and for years 2 through 5. In addition, in estimating the effect of guideline-based treatment, patients who survived less than 4 months and whose reason for nonadherence was stated as “patient expired” were excluded, because this would have biased the effect of nonadherence away from the null. In the final model, those with military and private insurance were combined and no difference in survival was seen. Effect modification was also assessed for the relative risk of death associated with nonadherence according to comorbidity and age.

Results

Study Population

Table 2 lists characteristics of the study population according to adherence/nonadherence with NCCN Guidelines. Most patients received guideline-adherent treatment (n=559; 82.7%). Patients who received nonadherent treatment were 2.5 times as likely to die within 5 years of diagnosis (68.4% vs 27.7%); these patients also had significantly poorer survival time (first quartile: 7.2 vs 33.8 months).

Reasons for Nonadherence and Associated Comorbid Conditions

Of the 117 patients who received nonadherent treatment (data not shown), the 2 most common reasons that guideline-based treatment was not received were risk factors and comorbidities (n=35; 29.9%) and lack of recommendation of one or more treatment modalities included in the guidelines (n=34; 29.1%). These were followed by patient/guardian refusal of treatment (n=26; 22.2%), death (n=11; 9.4%), and unknown treatment status (n=11; 9.4%). Of patients who received nonadherent treatment, the prevalence of comorbid conditions is shown in Table 3.

Nonadherence With NCCN Guidelines

Table 4 displays the risk ratios for nonadherence with NCCN Guidelines. Compared with patients who have no comorbidity, those with moderate/severe comorbidity had a 61% increased risk of being nonadherent (CIR, 1.61; 95% CI, 1.13–2.30). Compared with patients with private insurance, those who were uninsured had a 57% increased risk of nonadherence (CIR, 1.57; 95% CI, 0.95–2.59), although this result failed to reach statistical significance (P=.07). Patients with rectal cancer (P=.06), older patients, and those with higher disease stage had increased risks of receiving nonadherent treatment.

Overall Survival

The results of the survival analysis for the relative risk of all-cause mortality are depicted in Table 5. In evaluating the effect of guideline nonadherence on the risk of death, in year 1, patients with nonadherent treatment had 3.6 times the risk of death (HR, 3.55; 95% CI, 2.16–5.85) compared with those who received guideline-adherent treatment. For years 2 through 5, nonadherence was associated with an 80% increased risk of death (odds ratio [OR], 1.80; 95% CI, 1.14–2.83). Patients with moderate/severe
comorbidity had a 60% increased risk of death (HR, 1.60; 95% CI, 1.15–2.23). Uninsured patients, patients with higher disease stage, and those with high/unknown tumor grade had increased risks of death. Some evidence showed that patients with Medicaid and Medicare had increased risks of death; however, these results were not statistically significant.

Table 6 depicts the results of the stratified analysis regarding the association between treatment nonadherence and all-cause mortality according to comorbidity and age. The detrimental effect of nonadherence declined with increasing comorbidity and varied according to age. Consistent with the overall results, the higher risk associated with nonadherence was found in the first year after diagnosis. The exception for this occurred in the oldest category, in which a higher risk of mortality was seen in years 2 through 5.

**Discussion**

Several factors predicted nonadherence with NCCN Guidelines and overall survival for patients with
CRC. Patients with moderate/severe comorbidity had a significantly increased risk of nonadherence. This is consistent with reported results for nonadherence specifically by Chagpar et al.12,25,27,35,44 In many cases, deviating from NCCN Guidelines is clinically justified, because comorbid disease may be a contraindication for treatment and increase the risk of serious adverse events.35,45 However, other studies have shown that patients with comorbidity do not experience an increased number of treatment-related adverse events46 and also derive a benefit from receiving neoadjuvant/adjuvant chemotherapy/radiation.21 In the stratified analysis across levels of comorbidity, patients who received nonadherent treatment at all levels of comorbidity had increased risks of death. This demonstrates that careful consideration should be given to providing treatment options to all patients unless clear reasons exist to deviate from NCCN Guidelines.

Concern has been expressed regarding the association between advancing age and the decreasing likelihood of receiving neoadjuvant/adjuvant therapy.42,43,47 A reason for these findings has been the increasing prevalence of comorbid disease in older age groups. Consistent with the literature,10,38,42,43,47–52 the investigators found that even after controlling for comorbidity, those aged 65 to 74 years and 75 to 85 years had significantly higher risks for treatment nonadherence compared with adults aged 50 to 64 years. This finding is concerning because many of these patients have a considerable life expectancy at the age of cancer diagnosis.21 In addition, fit elderly adults with CRC have been shown to tolerate and derive similar benefit from chemotherapy as younger adults.15,16 Similar to the effect reported for comorbidity, nonadherence was associated with an increased risk of death across age categories. The NCCN Guidelines regarding the administration of chemotherapy for patients with stage II–IV CRC outline several chemotherapy protocols to be considered for patients in whom toxicity is a concern with combination oxaliplatin-based therapies.67 The fact that advancing age is associated with an increasing risk of nonadherence does not necessarily imply that physicians are responsible for the lack of adherence. Of all nonadherent patients, 22% refused treatment. However, why guideline-based treatment was not recommended for 29% of nonadherent patients is unknown.

Uninsured patients had an increased risk of nonadherence, although this result failed to reach statistical significance. As other investigators have noted,53 patients without insurance are less likely to receive chemotherapy/radiation because these treatments can be expensive and, without remuneration, the costs must be absorbed by the treating facility. Ideally, with the implementation of the Affordable Care Act (ACA), uninsured patients will no longer have this barrier to receiving high-quality cancer care. However, insurance status may be simply one component in determining whether an individual receives guideline-adherent treatment.54 Notably, African Americans did not show an increased risk of nonadherence. Other investigators have also reported that race is not a factor in receiving treatment for CRC.9,25 However, most of the evidence has shown that African Americans are less likely to receive treatment for CRC.23,26,42–44,51,55–58

Patients with rectal tumors and those with stages II–IV CRC had increased risks of nonadherence. NCCN Guideline–concordant treatment for stage II/III rectal cancer involves surgery plus neoadjuvant/adjuvant chemoradiation,7 which increased the likelihood of nonadherence compared with those with colon cancer. Likewise, according to the NCCN Guidelines for Colon/Rectal Cancers, increasing tumor stage is associated with neoadjuvant/adjuvant chemotherapy and/or radiotherapy,6,7 thus increasing the likelihood of nonadherence, which was also reported by Chagpar et al.9

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>27</td>
<td>23.1</td>
</tr>
<tr>
<td>Fluid and electrolyte disorders</td>
<td>23</td>
<td>19.7</td>
</tr>
<tr>
<td>Weight loss</td>
<td>22</td>
<td>18.8</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>14</td>
<td>12.0</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>11</td>
<td>9.4</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>5</td>
<td>4.3</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Psychoses</td>
<td>3</td>
<td>2.6</td>
</tr>
<tr>
<td>Blood loss anemia</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Deficiency anemia</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>2</td>
<td>1.7</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Neurodegenerative disorders</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Paralysis</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>Pulmonary circulation disorders</td>
<td>1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table 3 Comorbidities Associated With Nonadherence (N=117)
The importance of adherence with NCCN Guidelines is demonstrated by the poorer prognosis of patients who did not receive guideline-based treatment. The effect of nonadherence on overall survival was greatest in the first year after diagnosis, with nonadherent patients having 3.6 times the risk of death. For years 2 to 5, nonadherent treatment was associated with an 80% increased risk of death.

The importance of guideline-based treatment in this study was much more prominent than in the study reported by Boland et al, who found that nonadherence in high-risk patients with stage II and III colon cancer was associated with a 43% and 88% increased risk of death, respectively.

The importance of primary and secondary prevention of CRC through adoption of and compliance with screening guidelines is unequivocal, with studies repeatedly showing that screening for CRC reduces incidence, morbidity, and mortality associated with the disease. However, this does not change the fact that 80% to 91% of adults diagnosed with CRC are not diagnosed via screening modalities. Although an extensive amount of research has been devoted to increasing the uptake of screening guidelines, comparatively little effort has focused on improving the care of patients after diagnosis. As noted by Marshall et al, “Numerous improvement programs have been implemented to increase CRC screening rates, but few have focused on improving the care and management of patients with a diagnosis of this malignancy.” This reality exists despite the 1999 report, “Ensuring Quality Cancer Care,” by the National Cancer Policy Board (NCPB), which highlighted their findings in the following statement: “The NCPB has concluded that for many Americans with cancer, there is a wide gulf between what could
be construed as the ideal and the reality of their experience with cancer care. Thus, from a health equity perspective, providing access to high-quality cancer care for all patients is critically needed.

As a practical recommendation moving forward, the results of this study highlight the need for improved physician-patient communication during the clinical encounter to inform the treatment plan. Shared decision-making is particularly important for patients with stage II colon cancer and those with stage IV CRC. High-risk patients with stage II colon cancer require a discussion of the risks and benefits of receiving chemotherapy and surgery versus surgery alone. In contrast, for patients with stage IV CRC, the model of shared decision-making is important when considering the option to forego chemotherapy and receive only supportive care. Based on life expectancy at the time of diagnosis, presence of comorbid disease, and quality-of-life considerations, patients and their oncologists may justifiably decide against chemotherapy, and thereby deviate from treatment guidelines. However, and barring the presence of severe comorbid conditions, interventions are needed to improve adherence to treatment guidelines among patients with stage II/III rectal cancer and those with stage III colon cancer to ensure that they receive the highest quality of care. Patient navigation has been shown to be an effective intervention to remove barriers to patient adherence earlier in the cancer care continuum. However, up to this point, the effect of navigation on improving outcomes during the treatment phase of care has been mixed. The impact of health care policy, namely the ACA, on removing lack of health insurance as a barrier to receiving guideline-adherent treatment could be assessed in future studies.

Additional factors associated with overall survival after diagnosis were comorbidity, payer type, and the tumor-related factors of disease stage and tumor grade. Most of the literature has shown that increasing comorbidity predicts a poorer prognosis. For payer type, findings showing an increased risk of death among uninsured patients is consistent with the results reported by Boland et al. Lack of insurance is associated with lower SES, which has been consistently implicated as a cause of cancer health disparities. Although some evidence showed that patients on Medicaid had an increased risk of death, this result did not approach statistical significance, which differs from that reported by Boland et al.

This study had several strengths. Comorbidity information is not routinely available in retrospective cohort studies of cancer outcomes. This information allowed the investigators to examine the effect of comorbidity and age with adjustment for both variables in assessing the relationship with guideline non-adherence. Physician documentation was also available on why patients did not receive guideline-adherent treatment. An index of the Elixhauser comorbidity instrument was used, as described by van Walraven et al. This index was developed for the outcome of in-hospital death and is particularly germane for the assessment of guideline-adherent treatment, because only comorbid conditions severe enough to have an impact on short-term mortality should prohibit a patient from receiving recommended treatment.

Some study limitations should be considered. This study was conducted at 1 institution, and therefore the findings may not be generalizable to other regions of the United States. Although adherence with guideline-based treatment was high in this study (82.7%), it should not necessarily be inferred that patients who did not undergo guideline-adherent treatment received inferior care. Among the 34 nonadherent patients (29.0%) whose recommended treatment was not consistent with guidelines, there could have been medically justifiable reasons a particular treatment was not provided, which were not documented in the registry database. This study's definition of nonadherence was defined as undertreatment. After discussion with the oncologist, patients with stage II colon cancer may decide to receive chemotherapy, which is consistent with NCCN Guidelines. Therefore, these patients were not considered overtreated.

An additional limitation concerns the analysis of overall survival with death from any cause as the outcome. Information on the cause of death was not available, which is a common limitation of registry studies. Although overall survival is considered the most important end point in medical oncology, it is confounded by deaths from other causes. However, overall survival is an unbiased end point. That is, the assessment of death is objective. Conversely,
it may not always be clear when the cause of death is cancer-related. For example, cancer could play a large contributory role in death from comorbid conditions because of a decreased ability to compensate for the overall burden of morbidity resulting from the combined effects. Adverse effects of treatment could have a similar effect on other direct causes of death that seemed to be unrelated to the cancer or its treatment. The impact of non–cancer-related causes of death is shown in Table 6. With increasing comorbidity, the proportion of non–cancer-related deaths also increases. Therefore, the impact of nonadherence to guideline-based treatment, which, in theory, has no or minimal effects on non–cancer-related causes of death, decreased with increasing comorbidity, because more deaths were from non–cancer-related causes. Ideally, CRC-related death would be a more sensitive measure of the detrimental effect of guideline-based treatment nonadherence and the higher risk of cancer-related death. Future studies with accurate information on the primary cause and contributory causes of death could examine the effect of nonadherence on overall survival compared with cancer-specific survival. Lastly, consistent information on subcategories of disease stage was not available, and subcategories were combined into one stage grouping. The investigators acknowledge that heterogeneity of individual prognoses exists within stage, and emphasize that they reported the average effect according to disease stage.

Conclusions

The results of this study identified patient characteristics associated with an increased likelihood of nonadherence with NCCN Guidelines for CRC, and emphasize the importance of receiving guideline-adherent treatment as a major factor impacting prognosis. Results showed that increasing age continues to be associated with an increased risk of nonadherence, even after adjustment for comorbidity. In addition, although certain comorbid conditions are contraindications to treatment, patients with comorbid conditions that are not contraindications may still benefit from receipt of guideline-concordant treatment. Consistent with other reports,8,9 these results highlight the importance of receiving high-quality treatment, which this study defined as adherence to NCCN Guidelines. The care that patients receive

<table>
<thead>
<tr>
<th>Table 6 Adjusted Hazard Ratios for Nonadherence with All-Cause Mortality Stratified by Comorbidity Status and Age</th>
</tr>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Guideline treatment</td>
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<tr>
<td>No</td>
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</table>

Abbreviations: HR, hazard ratio; Ref, reference group.
*Adjusted for race, age, disease stage, and tumor grade.
*Adjusted for comorbidity, payer type, age, disease stage, and tumor grade.

after diagnosis has been the focus of recent investigations, but much more research is needed to bridge the gap between the best possible cancer care and the care that many patients with CRC receive.

References


Hines et al


