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Non-Adherence to Standard of Care for Locally Advanced Colon Cancer as a Contributory Factor for High Mortality Rates in Kentucky

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Abstract

Introduction: Kentucky has one of the highest mortality rates in colon cancer despite dramatic improvements in screening. The National Comprehensive Cancer Network (NCCN) guidelines recommend surgery and adjuvant chemotherapy for locally advanced (stage IIB/c and stage III) colon cancer (LACC). The purpose of this study was to determine the rate of non-adherence with current standard of care (SOC) and associated factors as possible contributors to mortality.

Methods: The Kentucky Cancer Registry (KCR) database linked with administrative health claims was queried for individuals (> 20 years) diagnosed with LACC from 2007–2012. Bivariate and logistic regression of non-adherence was performed. Survival analysis was performed with Cox regression and Kaplan-Meier plots.

Results: A total of 1404 patients with LACC were included. Approximately 42% of LACC patients were noted to be non-adherent to SOC with nearly all (95.7%) failing to receive adjuvant chemotherapy. After adjusting for all significant factors, we demonstrated factors associated with non-adherence included: age >75 years, stage III colon cancer, high Charlson comorbidity index (CCI 3+), low poverty level, Medicaid coverage, and disability. Adherence to SOC is associated with a significant improvement in the 5-year survival rate compared with non-adherence (63.0% vs 27.4%, respectively, $p < 0.0001$).

Conclusion: Our study identified multiple factors associated with the failure of LACC patients to receive SOC, particularly adjuvant chemotherapy, suggesting the need to focus on improving

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adjuvant chemotherapy compliance in specific populations. Non-adherence to LACC SOC is likely a major contributor to the persistently high mortality rates in Kentucky.

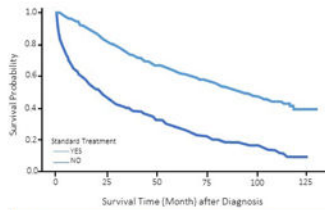
Precis

This study identified multiple factors associated with failure of locally advanced colon cancer (LACC) patients to receive standard of care, particularly adjuvant chemotherapy, suggesting the need to focus on improving adjuvant chemotherapy compliance in specific populations. Non-adherence to LACC standard of care is likely a major contributor to persistently high mortality rates in Kentucky.

Graphical Abstract

Non-Adherence to Standard of Care for Locally Advanced Colon Cancer as a Contributory Factor for High Mortality Rates in Kentucky

Standard of Care: Surgical resection followed by adjuvant chemotherapy within 6 months of completion of surgery in stage III disease, stage IIb (prior to 2010) and stage IIb/c (after 2010)



AGE 65-74 5x more likely to be non-adherent compared to 20-49	STAGE Stage IIb/c 2.7x more likely to be non-adherent compared to Stage IIIa/b	CCI Group 3+ 3x more likely to be non-adherent compared to CCI 0
DISABILITY Disabled patients 3x more likely to be non-adherent compared to non-disabled	MEDICAID Medicaid patients 2.7x more likely to be non-adherent compared to privately insured	POVERTY Moderate and high poverty 1.4x more likely to be non-adherent compared to lower poverty

Data source: The Kentucky Cancer Registry, Jan 2007 – Dec 2012

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INTRODUCTION

Local and regional colorectal cancer (CRC) accounts for more than 55% of all CRC diseases^(1, 2). Locally advanced colon cancer (LACC) is defined as stage IIb/c and stage III colon cancer, in which adjuvant chemotherapy is recommended by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guideline in Oncology. The NCCN practice guidelines are widely accepted by healthcare providers secondary to its vast benefit on patient survival and currently considered the standard of care (SOC) in treating CRC^(3, 4). Currently, the NCCN recommends surgical resection followed by adjuvant chemotherapy for patients diagnosed with resectable nodal-positive stage III disease and judicious use of adjuvant chemotherapy for nodal-negative stage II colon cancer with high risk features, such as lymphovascular invasion and perineural invasion⁽⁵⁾. Secondary to advancements in multidisciplinary care, including adjuvant chemotherapy, the 5-year survival for patients with LACC has increased significantly over the last 30 years with survival rates rising from 54.8% to 60.9% in right colon cancer and 56.9% to 66.9% in left colon cancer⁽⁶⁾.

CRC is currently the third leading cause of cancer related mortality in the United States⁽⁷⁾. According to the American Cancer Society, Kentucky has one of the highest CRC incidence rates in the nation⁽²⁾. The incidence was 59.6 per 100,000 for Caucasian males and 43.5

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per 100,000 for Caucasian females between 2009 and 2013. In addition, Kentucky ranked fifth in CRC mortality from 2010–2014⁽²⁾. Nearly half of the 120 counties (54) in eastern Kentucky are in central Appalachia, which is characterized by extreme poverty, rurality and low socioeconomic status⁽⁸⁾. The eastern Kentucky Appalachia population historically carries a worse CRC mortality rate (21.6 per 100,000) compared to its urban non-Appalachian counterpart (20.4 per 100,000)⁽⁹⁾.

It is particularly challenging to deliver healthcare to residents of eastern Kentucky Appalachia due to lack of access, resources and low health literacy. Beginning in 1999, Kentucky implemented several programs to expand CRC screening by addressing two major barriers including lack of insurance coverage and lack of provider recommendations^(10–14). Dignan et al⁽¹⁵⁾ implemented a module among participating health care providers to increase CRC screening, especially in rural Kentucky. The Affordable Care Act Medicaid expansion in Kentucky was another substantial effort to increase screening and decrease CRC mortality. Gan et al⁽¹⁶⁾ previously conducted a population study to investigate the influence of Affordable Care Act expansion on CRC screening in Kentucky, and found it to positively impact colonoscopy screening, diagnosis and survival with a more profound benefit among the Appalachian Kentuckians. These focused interventions led to an increase in the CRC screening rate in Kentucky from 34.7% in 1999 to 70.1% in 2016^(10, 12). However, even with these measures, CRC mortality remains high in Kentucky.

Previous studies demonstrated a survival benefit in patient adherence to SOC and suggested several risk factors, such as low socioeconomic status and patient comorbidities, associated with non-adherence to SOC^(17–19). Limited research has identified risk factors specifically associated with LACC SOC non-adherence⁽⁴⁾. The purpose of this study was to determine the non-adherence rate and associated risk factors to SOC among LACC patients in Kentucky. We found Medicaid insurance status and poverty both contributed to LACC SOC non-adherence, with adjuvant chemotherapy noncompliance as the most significant contributory factor. The LACC SOC non-adherence was found to be a prognostic factor associated with a worse 5-year survival.

PATIENTS AND METHODS

Data Sources

De-identified health claims linked Kentucky Cancer Registry (KCR) dataset was extracted for CRC patients diagnosed between January, 2007 and December, 2012. Institutional Review Board approval was obtained from the University of Kentucky's Office of Research prior to data analysis. To ensure the data accuracy, only patients with at least 13 months of health insurance continuous enrollment (6 months prior to cancer diagnosis to 6 months after, excluding the month of diagnosis) were included in the study. Patients who met the following criteria were included in the study: (1) adult patients age greater than 20 years old; (2) current Kentucky residents; (3) first primary colon cancer diagnosis; (4) diagnosed with stage b (prior to 2010) or stage IIb/c (after 2010), and any stage III colon cancer; (5) receiving adjuvant chemotherapy treatment within 6 months of surgical resection. Pathological staging and diagnosis of colon cancer was captured through the

Current Procedural Terminology codes. A data use agreement was obtained between the investigator and KCR prior to launch of the study.

The following demographic variables were included in our analysis through the IRB approved collaboration with the KCR: age at diagnosis, race, sex, education attainment, poverty status, rural status, Appalachian status, disability status, insurance type, treatment hospital type and distance to treatment facility. Education attainment and poverty status was determined by high school completion rate and percentage of population below poverty income within the 2000 Census tract. Education attainment was categorized into three levels based on the tertiles of corresponding distributions: low education group (high school completion rate less than 67.9%); moderate education group (high school completion rate between 67.9% and 79.2%), and high education group (high school completion rate of 79.2% or higher). High poverty level group reside in areas with 18.9% or more of the population below poverty income, while low poverty level patients live in areas with less than 9.7% of the population below poverty income. Appalachian status was determined by the county-level status according to the Appalachia Regional Commission, as the 54 counties in Eastern Kentucky⁽⁸⁾. Rurality status was based on the Urban-Rural Continuum codes with the values of 1–3 as urban and 4–9 as rural⁽²⁰⁾. The patient's disability status was defined using the corresponding variables from claim sources. For Medicaid patients, long term disability coverage was considered as disabled. The type of hospital was categorized as large academic hospital (University of Louisville and University of Kentucky), large non-academic hospital (reporting ≥ 100 cancer cases per year), small non-academic hospital (reporting < 100 cancer cases per year), and out-of-state hospital. Since the institute of the specialist was de-identified, we utilized distance from the registered residence to the hospital where patients received treatment to calculate great circle distance, proposed by the North American Association of Cancer Care Registry⁽²¹⁾.

The following clinical variables were also included: stage, tumor grade, and Charlson comorbidity Index (CCI). The CCI was calculated using the modified version for claim data and categorized into four categories (0, 1, 2 and 3+)⁽²²⁾. Adequacy of surgical resection was evaluated based on sufficient number of lymph nodes examined during pathological evaluation. Surgical resection was deemed adequate if 12 or more lymph nodes were resected during surgery. Stage IIb/c and stage III colon cancer and tumor grade were defined using the American Joint Committee on Cancer (AJCC) staging manual⁽²³⁾. The AJCC seventh edition published an updated TN categorization for colon cancer in 2010 to designate stage II with high risk features, previously as stage IIb, into stage IIb/c colon cancer⁽²⁴⁾. In our study, we recognized that stage IIb/c became a new stage designation in 2010 and a proportion of our data was collected prior to this date. There was no high-risk feature data available prior to 2010, and collection of high risk features based on pathology reports was incomplete after 2010. The NCCN practice guideline has recommended use of adjuvant chemotherapy in stage II colon cancer with high-risk features, such as high grade, T4 disease, lymphovascular invasion, inadequate or positive margin, insufficient lymph node evaluation, perineural invasion, tumor deposits, and perforation⁽⁵⁾. We defined adherence to SOC in our study as surgical resection followed by adjuvant chemotherapy within 6 months of completion of surgery in stage III disease, stage IIb (prior to 2010) and stage

IIb/c (after 2010). Deviations from SOC include not receiving surgical resection or adjuvant chemotherapy in LACC disease.

Statistical analysis

We extracted information of patient treatment status from insurance billing codes. LACC patients who did not receive surgery, or adjuvant chemotherapy, or both, were considered non-adherent to SOC. A descriptive analysis of the demographic and clinical factors was performed. We used χ^2 tests to examine associations between non-adherence to SOC and variables described above in the bivariate analysis. Logistic regressions were fitted to identify significant factors associated with non-adherence while controlling for other covariates. Cox regression survival analysis was performed and Kaplan-Meier curve was plotted based on the life table. All analyses were performed using Statistical Analysis System software version 9.4 (Statistical Analysis System Institute, Inc., Cary, North Carolina, USA). All statistical tests were two sided with a p-value ≤ 0.05 to identify statistical significance.

RESULTS

Distribution of non-adherence to LACC SOC

A total of 1,404 patients met the inclusion criteria. Two large academic hospitals, 38 large non-academic hospitals and 60 small non-academic hospitals were included. Our data provided lymph node yield data for 1,393 patients, in which 1,169 patients (83.9%) had 12 or more lymph nodes examined in final surgical pathology. Out of the 1,404 patients, 215 patients were diagnosed with stage IIb/c, 832 patients with stage IIIa/b and 357 patients with stage IIIc colon cancer. A total of 588 patients (41.9%) were considered non-adherent to LACC SOC. It was found that 60.5% of stage IIb/c colon cancer patients were considered non-adherent, while non-adherence rates to stage IIIa/b and stage IIIc were 38.2% and 39.2%, respectively (Table 1). Among the 130 stage IIb/c non-adherent patients, 15 (11.5%) did not receive surgery and 115 (88.5%) did not receive adjuvant chemotherapy. The majority of the stage III non-adherence (97.8%) was attributed from failure to receive adjuvant chemotherapy. Only 10 out of 448 patients (2.2%) did not receive surgery in stage III disease. Combining all stages, we found that the majority (95.7%) of non-adherence to SOC was attributed from adjuvant chemotherapy noncompliance with a minor percentage (4.3%) of patients that did not receive surgical resection (Table 2).

Patient characteristics and risk factors associated with non-adherence to SOC using bivariate analysis

Out of the 1,404 patients included in our study, we found several patient characteristics associated with non-adherence to SOC in the bivariate analysis. Our data suggested that elderly patients ≥ 75 years old have a higher non-adherence rate (65.0%) compared to other age subgroups (12.3% in 20 to 49 years old, 20.0% in 50 to 64 years old, and 26.5% in 65 to 74 years old, $p < 0.0001$). Females were more likely to be non-adherent compared to males (44.8% vs. 38.3%, $p = 0.013$). We did not observe any significant difference among Caucasians, African-Americans and other ethnicity subgroups. Stage IIb/c had a significantly higher non-adherence rate compared to stage IIIa/b and IIIc disease.

Tumor grade, which was also used to categorize disease burden along with tumor stage, was found to be statistically different. The highest non-adherence rate was found in the well-differentiated subgroup (52.1%) while the lowest non-adherence rate was found in the moderately-differentiated subgroup (39.2%, $p=0.0185$). The CCI was found to be another patient functional status indicator, besides advanced age and disease burden, associated with non-adherence to SOC. Patients with increasing CCI scores had corresponding increasing non-adherence rates (34.0% for CCI 0, 44.2% for CCI 1, 48.8.0% for CCI 2, and 66.7% for CCI 3+, respectively, $p<0.0001$). The majority of the patients included were non-disabled. The bivariate analysis found a higher non-adherence rate in the non-disabled subgroup compared to the disabled subgroup (45.8% vs. 36.8%, $p<0.0001$) (Table 3).

From a socioeconomic perspective, we found insurance status to be a statistically significant factor associated with non-adherence. Our study population consisted of a predominant 80.1% Medicare, 15.9% privately-insured and 4.0% Medicaid patients. Medicare and Medicaid insurance subgroups had higher non-adherence rates (46.3% and 44.6%, respectively) compared to the privately insured subgroup in the bivariate analysis (18.8%, $p<0.0001$). Other factors such as education attainment, poverty level, Appalachian status, rurality, great circle distance to hospital and hospital types were not statistically significant in the bivariate analysis (Table 3).

Patient characteristics and risk factors independently contributing to non-adherence to SOC using logistic regression analysis

After adjusting for all variables, logistic regression analysis suggested that age, stage, CCI, disability status, Medicaid insurance status and poverty level were independently associated with non-adherence to LACC SOC. Patients in age group 65–74 years-old and age group > 75 years-old were more likely to be non-adherent compared to patients in age group 20–49 years-old (Odds Ratio (OR) 4.6, Confidence Interval (CI) 1.8–11.7, $p=0.0013$, and OR 25.8, CI 10.2–65.4, $p<0.0001$, respectively). Stage IIb/c patients were more likely to be non-adherent to LACC SOC compared to Stage IIIa/b patients (OR 2.7, CI 1.9–3.9, $p<0.0001$). Patients with significant comorbidities in the CCI 3+ group were also more likely to exhibit non-adherence compared to patients without comorbidities (OR 3.2, CI 2.1–4.8, $p<0.0001$). The disability status was more likely to exhibit non-adherence to SOC compared with non-disabled patients after controlling for other significant variables (OR 2.9, CI 1.6–5.5, $p=0.0009$) (Table 4).

Medicaid status remained a strong independent factor in contributing to non-adherence of LACC SOC. Patients in the Medicaid subgroup were more likely to have non-adherence in contrast to privately-insured patients (OR 2.7, CI 1.5–4.6, $p=0.0004$). Poverty level was also found to be a contributing factor to non-adherence in the logistic regression analysis. Patients in the moderate and high poverty subgroup were more likely to be non-adherent to LACC SOC compared to the low poverty subgroup (OR 1.4, CI 1.0–1.9, $p=0.034$ and OR 1.4, CI 1.0–1.9, $p=0.036$, respectively) (Table 4).

Patient characteristics and risk factors contributing to LACC mortality

Adherence status to LACC SOC, age, stage, tumor grade, CCI, and disability status were associated with patient survival in the Cox regression multivariate analysis. Sex, poverty level, Appalachian status, insurance status, and hospital types were not correlated with worse survival. Cox regression analysis demonstrated that non-adherence to SOC contributed to increased mortality (Hazard Ratio (HR) 2.4, 95% CI 2.0–2.8, $p < 0.0001$) (Table 5). Kaplan-Meier curves demonstrated a survival benefit in those adherent to SOC (Figure 1). The 5-year survival rate was 63.0% and 27.4% for patients in adherence and non-adherence groups, respectively. Advanced age also had worse survival compared to younger patients (HR 2.1, 95% CI 1.3–3.5 in 65–74 years old subgroup, and HR 2.9 1.7–4.8, in greater than 75 years old subgroup, respectively). Disease-specific factors contributing to survival rate included advanced stage and poor tumor grade. Stage IIb/c and stage IIIa/b subgroups both had better survival compared with the stage IIIc subgroup (HR 0.7, CI 0.6–0.8 for stage IIb/c and HR 0.6, CI 0.5–0.7 for stage IIIa/b, $p < 0.0001$). Additionally, the moderately and poorly differentiated subgroup had worse survival compared to the well differentiated subgroup (HR 1.8, CI 1.2–2.8 for moderately differentiated, and HR 2.1, CI 1.3–3.3 for poorly differentiated, $p = 0.0002$). Patients with greater CCI, specifically 2 and 3+, had worse survival than patients without comorbidities (HR 1.3, CI 1.1–1.6 for CCI 2 and HR 2.0, CI 1.6–2.5 for CCI 3+, $p < 0.0001$). Finally, disability status was another patient functional status factor that contributed to worse survival compared with the non-disabled population (HR 1.6, CI 1.2–2.1, $p = 0.0039$) (Table 5).

DISCUSSION

Novel treatment options have dramatically improved 5-year survival rates in patients with CRC, increasing from 58% in 1980 to 77% in 2000⁽²⁵⁾. Non-adherence to the NCCN guidelines for CRC treatment have been reported to range from 10% to 35%^(26–29). Notably, our study demonstrated a 42% non-adherence rate to LACC SOC treatment in Kentucky, which is higher compared to other studies. We found that failure to provide adjuvant chemotherapy was the major contributing factor to non-adherence to SOC in Kentucky with Medicaid status and poverty level as the two primary socioeconomic factors contributing to this non-adherence.

In our current study, we found that patients with Medicaid were 2.7 times more likely to exhibit non-adherence to LACC SOC compared to privately-insured patients (Table 4). This was consistent with previous studies where patients who required government-subsidized insurance programs were associated with decreased adherence to SOC^(4, 30). From our study, 22 out of 25 Medicaid patients (88%) in the LACC SOC non-adherence group was secondary to failure to receive adjuvant chemotherapy. Warren et al⁽³⁰⁾ found that patients who had Medicaid-subsidized Medicare insurance were 8% less likely to have a medical oncologist consultation compared to Medicare or Medicare subsidized with private insurance. They hypothesized that this was due to limited access to physicians accepting Medicaid⁽³⁰⁾. A survey administered to 2,218 physician participants in 2012 revealed that 36% of these physicians were not accepting Medicaid insurance⁽³¹⁾. Healthcare system navigation has been shown to increase patient access for these at risk patients^(32–34). Our

underserved Kentucky population, where Medicaid enrollment (30.0%) is higher compared to the national average (22.2%), would benefit from interventions such as, increasing healthcare access, drug delivery systems, social supports, and patient navigators to improve adherence to LACC SOC^(35, 36).

Another socioeconomic factor found to be associated with non-adherence to LACC SOC was poverty level, defined by percentage below poverty income indicated in the 2000 Census tract. Poverty was associated with Medicaid insurance status, which required individual income to be below the 133% federal poverty level to qualify for Medicaid enrollment in Kentucky⁽³⁷⁾. Various studies have found that patients who were categorized as low income, defined using state poverty income as a reference, were less likely to receive chemotherapy compared to their higher income counterparts^(38–40). Our data, similar to these findings, also demonstrated that patients in the high poverty level subgroup (reside in area at least 18.9% population below poverty income) were 1.4 times more likely to be non-adherent than those in the low poverty level subgroup (reside in area less than 9.7% population below poverty income). This is particularly relevant to our economically-distressed, eastern Kentucky Appalachia population that suffers from the highest poverty rate and lowest per capita income of all Appalachian counties⁽⁴¹⁾. Therefore, the target population to improve adherence to LACC SOC is among the impoverished and those receiving Medicaid, which represent two common characteristics of the Kentucky Appalachian population^(8, 42).

We found that the 95.7% of all non-adherence to SOC was attributed to adjuvant chemotherapy non-compliance. The benefit of adjuvant chemotherapy in LACC was studied in multiple clinical trials, such as the Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer trial^(6, 35). A systematic review of 22 published studies concluded that non-adherence rates to adjuvant chemotherapy ranged from 29–61% in stage III colon cancer patients⁽⁴³⁾. This wide range could be due to variation in sample size and the quality of the database used in each study. The most recent Surveillance, Epidemiology, and End Results Medicare database reported a 40% chemotherapy noncompliance in stage III disease⁽⁴⁴⁾. Our data obtained from KCR, which has been nationally recognized for its completeness and accuracy, identified a similar non-adherence rate to adjuvant chemotherapy of 42% in LACC patients⁽³⁹⁾. Previous studies have identified several factors including age, stage, and CCI, as contributors to chemotherapy non-adherence^(18, 45–47). Due to the retrospective nature of our study, we were not able to assess causation for adjuvant chemotherapy non-adherence in the Kentucky population. Although causation could not be concluded from our study, we did find a significant association of age, stage, and CCI with non-adherence to LACC SOC, most likely attributable to adjuvant chemotherapy non-compliance.

Advanced age remained a strong prognostic factor associated with chemotherapy non-adherence^(18, 36, 48, 49). Adjuvant chemotherapy was more likely to be withheld for patients age 75 or older due to increased comorbidities and chemotherapy intolerance^(18, 50), despite studies indicating a benefit of adjuvant chemotherapy for stage III colon cancer patients with advanced age^(36, 50–53). Another patient factor related to functional status was comorbidity index, which is a known prognostic factor for colon cancer. Patients with high CCI were less

likely to be adhere to adjuvant chemotherapy^(45–47). Current chemotherapy regimens, such as FOLFOX-4 and CLF-1, have significant toxicities^(26, 54, 55). With an aging population in the United States, the delivery of adjuvant chemotherapy to this population requires tailored approaches to address comorbidity, performance status, cognitive function and social supports⁽¹⁹⁾. These studies were largely consistent with our findings, where advanced age, stage and CCI were also associated with non-adherence to SOC. Newer delivery programs, such as home oral and intravenous chemotherapy, have been shown to promote adherence^[39]. This strategy could represent an opportunity to improve chemotherapy adherence in patients with low performance status and those unable to commute significant distances for treatment.

The clinical significance of adherence to SOC, particularly adjuvant chemotherapy use in treating LACC, is a clear and consistent survival benefit⁽³⁾. Risk factors we found that directly impacted patient survival included age, stage, grade, CCI, and disability status. Abundant studies have described these same variables as individually contributing to increased mortality of colon cancer^(3, 19, 36, 43, 45–51, 56); however, these variables are non-modifiable. After adjusting for all significant variables by Cox regression survival analysis, we found that adherence to SOC demonstrated an independent survival benefit compared to the non-adherence group in our study. The 5-year survival rate in the adherence group was 63.0%, whereas the non-adherence group demonstrated a significantly lower survival rate of 27.4% (Figure 1). Zhao et al⁽⁴⁾, using the Texas Cancer Registry database linked with Medicare, found the 5-year survival rates in the adherence group was 89% for stage II and 73% for stage III; while those in the non-adherence group were 77% and 55%, respectively⁽⁴⁾. Our study applied a similar method and found worse survival rates in both adherence and non-adherence groups. In comparison to the Texas population, our Kentucky population consists of the most impoverished and highly disease-burdened in the US, which contributed to increased non-adherence and worse survival rates in our study. In addition, we found a greater percentage difference (35.6%) between the adherence and non-adherence groups, compared to the Texas study (12% for stage II and 22% for stage III). This suggested that improving adherence to SOC in our population would have a more profound benefit on patient survival. In contrast to the non-modifiable risk factors, patient adherence to SOC is a modifiable and important prognostic factor. Therefore, improving LACC SOC adherence became particularly important in the eastern Kentucky Appalachia population, where CRC mortality rate remains high.

We have clearly identified a significant problem with adherence to LACC SOC in our patient population; however, there are several limitations to our current study. First, our patient population reflects the demographics of Kentucky, which is predominantly Caucasian (87.6%) and, therefore, limits our ability to discern potential racial disparities⁽⁵⁷⁾. Second, we were unable to conduct cause analysis in non-adherence specific to our population due to the retrospective nature of our study, but we were able to extrapolate potential causes through associations and used the available literature to support our claims. Thirdly, the great circle distance to nearest hospital was determined using the closest documented treatment facility, and specific evaluation by medical oncology specialist was not available to assess accessibility of adjuvant chemotherapy. Finally, we were not able to capture every patient with stage II disease appropriate for receiving adjuvant chemotherapy due to

unavailability of data. Stage II high-risk features were not available prior to 2010 and these high-risk features were incompletely captured from pathology reports after 2010. As a result of this limitation, stage II patients with high-risk features receiving surgical resection and adjuvant chemotherapy were excluded as part of the LACC SOC definition.

CONCLUSION

Kentucky CRC mortality remains one of the highest in the US. Our study found that non-adherence to SOC, especially administration of adjuvant chemotherapy, may be a major contributing factor to this persistently high CRC mortality. Importantly, we identified age, stage, CCI, disability status, Medicaid insurance and poverty to be associated with low non-adherence to SOC, with the majority (approximately 96%) related to failure to receive adjuvant chemotherapy after surgical resection. Future work is needed to increase adjuvant chemotherapy compliance in this highly-vulnerable targeted population.

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ABBREVIATIONS

NCCN	National Comprehensive Cancer Network
LACC	Locally Advanced Colon Cancer
SOC	Standard Of Care
KCR	Kentucky Cancer Registry
CCI	Charlson Comorbidity Index
CRC	Colorectal Cancer
AJCC	American Joint Committee on Cancer
OR	Odds Ratio
CI	Confidence Interval

HR Hazard Ratio

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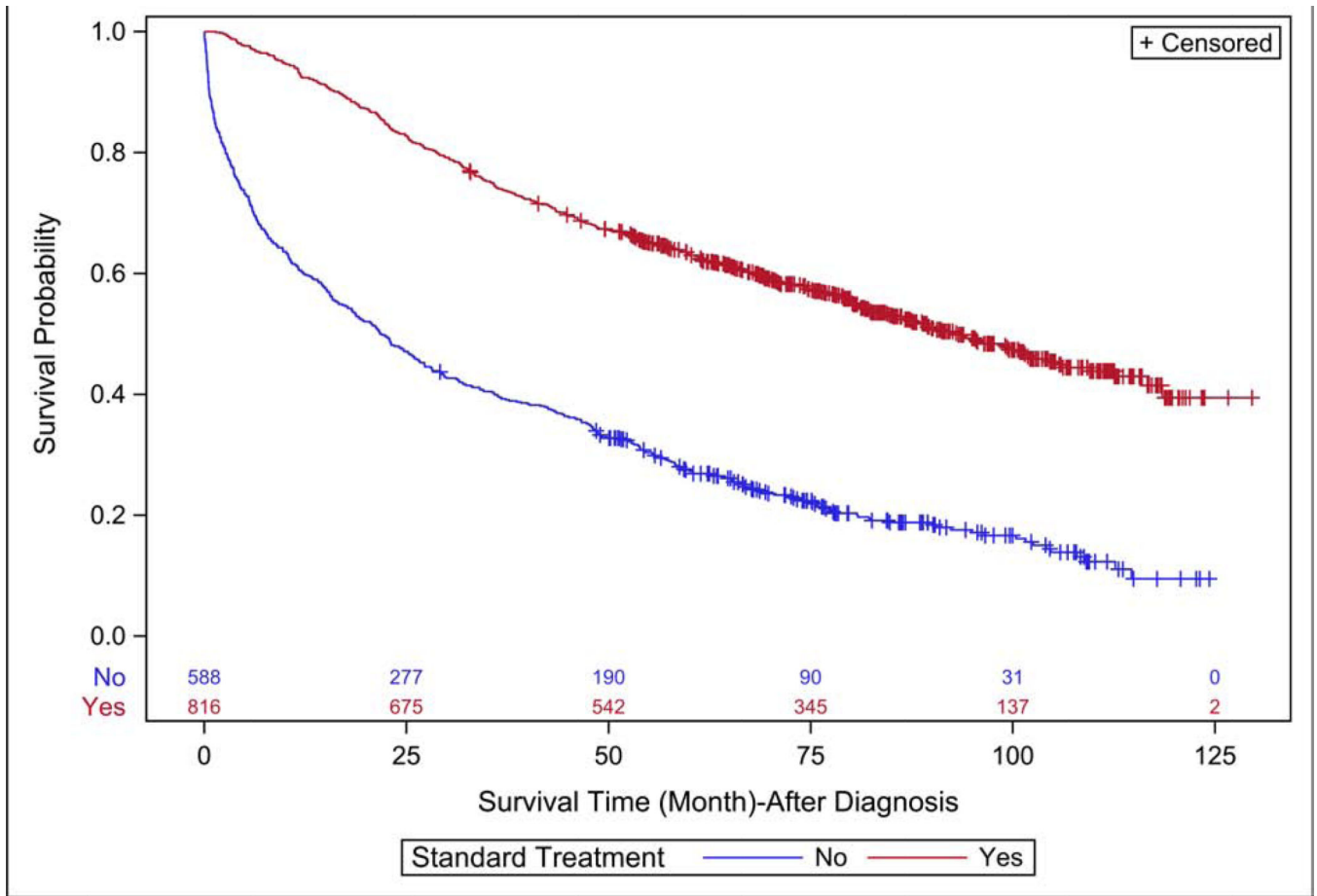


Figure 1. Comparison of Kaplan-Meier curves between adherence vs non-adherence group. The 5-year survival rates are 63.0% in the adherent group and 27.4% in the non-adherent group.

Table 1.

Distribution of Non-Adherence by Locally Advanced Colon Cancer Stage

Stage	Total, N	Adherent		Non-adherent	
		n	%	n	%
Stage IIb* or Stage IIb/c†	215	85	39.5	130	60.5
Stage IIIa, IIIb	832	514	61.8	318	38.2
Stage IIIc	357	217	60.8	140	39.2
Total	1404	816	58.1	588	41.9

* Stage IIb designation according to AJCC manual 6th edition prior to 2010

† stage IIb/c designation according to AJCC manual 7th edition after 2010

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Table 2.

Distribution of Non-Adherence Subgroups by Locally Advanced Colon Cancer Stage

Stage, non-adherence subgroup	n	%
Stage IIb* or Stage IIb/c [†]		
No surgery	15	11.5
No adjuvant chemotherapy	115	88.5
Stage IIIa, IIIb		
No surgery	9	2.8
No adjuvant chemotherapy	309	97.2
Stage IIIc		
No surgery	1	0.7
No adjuvant chemotherapy	139	99.3

* Stage IIb designation according to AJCC manual 6th edition prior to 2010

[†] stage IIb/c designation according to AJCC manual 7th edition after 2010

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Table 3.

Bivariate Analysis of Patient Demographics, Disease Burden Factors, and Socioeconomic Status/Rurality on Adherence to Locally Advanced Colon Cancer Standard of Care

Variable	Locally advanced colon cancer adherence rate to standard of care				p Value
	Non-adherence		Adherence		
	n	%	n	%	
Total	588	41.88	816	58.12	
Patient demographic					
Age					<0.0001*
20–49 y	9	12.33	64	87.67	
50–64 y	47	20.00	188	80.00	
65–74 y	124	26.50	344	73.50	
>75 y	408	64.97	220	35.03	
Race					0.1308
Caucasian	562	42.38	764	57.62	
African-American	25	35.71	45	64.29	
Other	1	12.50	7	87.50	
Sex					0.013*
Male	246	38.32	396	61.68	
Female	342	44.88	420	55.12	
Disease burden and patient functional status					
Stage					<0.0001*
Stage IIb [†] or Stage IIb/c [‡]	130	60.47	85	39.53	
Stage IIIa, IIIb	318	38.22	514	61.78	
Stage IIIc	140	39.22	217	60.78	
Grade					0.0185*
Well differentiated	25	52.08	23	47.92	
Moderately-differentiated	350	39.24	542	60.76	
Poorly differentiated	109	42.08	150	57.92	
Un-differentiated	82	49.40	84	50.60	
Grade unknown	22	56.41	17	43.59	
Charlson Comorbidity Index					<0.0001*
0	249	33.97	484	66.03	
1	156	44.19	197	55.81	
2	79	48.77	83	51.23	
3+	104	66.67	52	33.33	
Disable status					<0.0001*
Not disabled	495	45.79	586	54.21	

Variable	Locally advanced colon cancer adherence rate to standard of care				p Value
	Non-adherence		Adherence		
	n	%	n	%	
Disabled	71	36.79	122	63.21	
Unknown	22	16.92	108	83.08	
Socioeconomic status and rurality					
Insurance status					<0.0001*
Private insured	42	18.83	181	81.17	
Medicare	521	46.31	604	53.69	
Medicaid	25	44.64	31	55.36	
Education attained [§]					0.4648
Low	202	42.89	269	57.11	
Moderate	202	43.16	266	56.84	
High	184	39.57	281	60.43	
Poverty level ^{//}					0.1066
Low	178	37.95	291	62.05	
Moderate	207	44.04	263	55.96	
High	203	43.66	262	56.34	
Appalachia status ^{//}					0.9724
Non-Appalachia	399	41.91	553	58.09	
Appalachia	189	41.81	263	58.19	
Metro status [#]					0.3447
Rural	291	43.18	383	56.82	
Metropolitan	297	40.68	433	59.32	
Great circle distance to hospital ^{**}					0.1154
<10 miles	338	44.65	419	55.35	
10–50 miles	200	38.99	313	61.01	
>50 miles	28	40.58	41	59.42	
Unknown/out of state	22	33.85	43	66.15	
Hospital type ^{††}					0.3053
Academic hospital	18	41.86	25	58.14	
Large non-academic	457	41.51	644	58.49	
Small non-academic	91	46.67	104	53.33	
Out of state hospital	22	33.85	43	66.15	

* Statistically significant

[†] Stage IIb designation according to AJCC manual 6th edition prior to 2010

[‡] stage IIb/c designation according to AJCC manual 7th edition after 2010

[§] Education attainment is categorized as a range of patients who completed high school: low (75.8% to 84.3%), moderate (84.4% to 88.0%) and high (88.1% to 91.8%)

^{//} Poverty level is categorized into percentage below poverty income: high (above 18.7%), moderate (9.7% to 18.7%) and low (< 9.7%)

[¶] Appalachia status is defined by 54 counties in Eastern Kentucky belong to Appalachian Regional Consortium

[#] Metropolitan and rurality is defined based on Urban-Rural Continuum codes with the values of 1–3 as urban and 4–9 as rural

^{**} Great circle distance to hospital is the distance between patient residence to treatment hospital

^{††} Large hospitals are defined as treating >100 cancer cases per year; academic hospitals include University of Kentucky and University of Louisville

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Table 4.

Logistic Regression for Independent Risk Factors Associated with Non-Adherence to Standard of Care

Independent variable	Logistic regression analysis		
	Odds ratio	95% CI	p Value
Age			<0.0001*
20–49 y	Ref		
50–64y	1.32	0.59–2.95	0.5045
65–74 y	4.60	1.81–11.70	0.0013
> 75 y	25.80	10.18–65.37	<0.0001
Stage			<0.0001*
Stage IIb [†] or Stage IIb/c [‡]	2.7	1.9–3.9	<0.0001
Stage IIIa/b	Ref		
Stage IIIc	0.9	0.7–1.2	0.5949
Charlson Comorbidity Index			<0.0001*
Score 0	Ref		
Score 1	1.26	0.93–1.69	0.1324
Score 2	1.44	0.98–2.14	0.0652
Score 3+	3.18	2.09–4.83	<0.0001
Disability			0.0038*
Non-disabled	Ref		
Disabled	2.91	1.55–5.46	0.0009
Unknown	1.80	0.78–4.17	0.1713
Insurance status			0.0019*
Privately-insured	Ref		
Medicare	1.21	0.92–1.58	0.1678
Medicaid	2.66	1.54–4.60	0.0004
Poverty level [§]			0.0528*
Low	Ref		
Moderate	1.39	1.03–1.88	0.0340
High	1.40	1.02–1.91	0.0357

* Statistically significant

[†] Stage IIb designation according to AJCC manual 6th edition prior to 2010[‡] stage IIb/c designation according to AJCC manual 7th edition after 2010[§] Poverty level is categorized into percentage below poverty income: high (>18.7%), moderate (9.7% to 18.7%) and low (<9.7%)

Table 5.

Multivariate Cox Regression Survival Analysis.

Variable	Cox regression multivariate analysis		
	Hazard ratio	95% CI	p Value
Adherence to standard of care			<0.0001*
Adherent	Ref		
Non-adherent	2.37	2.03–2.77	
Age			<0.0001*
20–49 y	Ref		
50–64 y	1.30	0.84–2.02	
65–74 y	2.12	1.27–3.52	
>75 y	2.85	1.70–4.75	
Stage			<0.0001*
Stage IIb [†] or Stage IIb/c [‡]	0.68	0.55–0.84	
Stage IIIa/b	0.55	0.47–0.65	
Stage IIIc	Ref		
Grade			0.0002*
Well differentiated	Ref		
Moderately differentiated	1.80	1.17–2.78	
Poorly differentiated	2.07	1.32–3.25	
Un-differentiated	2.55	1.60–4.07	
Unknown	2.42	1.35–4.33	
Charlson Comorbidity Index			<0.0001*
0	Ref		
1	1.14	0.96–1.35	
2	1.30	1.05–1.60	
3+	2.02	1.64–2.48	
Disability			0.0039*
Not disabled	Ref		
Disabled	1.60	1.20–2.14	
Unknown	1.69	1.20–2.14	
Insurance status			0.2917*
Privately-insured	Ref		
Medicare	1.05	0.90–1.22	
Medicaid	1.26	0.94–1.70	
Poverty level [§]			0.2088*
Low	Ref		
Moderate	1.10	0.91–1.30	

Variable	Cox regression multivariate analysis		
	Hazard ratio	95% CI	p Value
High	0.94	0.77–1.15	
Appalachian status			0.8027 [*]
Appalachian	Ref		
Non-Appalachian	1.02	0.86–1.22	

^{*} Statistically significant

[†] Stage IIb designation according to AJCC manual 6th edition prior to 2010

[‡] stage IIb/c designation according to AJCC manual 7th edition after 2010

[§] Poverty level is categorized into percentage below poverty income: high (>18.7%), moderate (9.7% to 18.7%) and low (<9.7%).