



# The side of the primary tumor affects overall survival in colon adenocarcinoma: an analysis of the national cancer database

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## Abstract

**Background** Due to conflicting study results on the effect of laterality on overall survival in primary colon cancers, we sought to examine the impact of left compared to right-sided primary tumors on overall survival for stage I–III colon cancer using the largest dataset to date.

**Methods** The 2006–2013 NCDB was queried for patients with single primary, stage I–III colon adenocarcinoma and grouped by stage and tumor location.

**Results** For stage I–II tumors, 114,839 patients had resection (62% right:38% left). After adjustment, patients with right-sided tumors had superior survival ([HR right as reference]: 1.13, 95% CI 1.09–1.17,  $p < 0.001$ ). For stage III tumors, 71,024 patients had resection, (59% right:41% left). After adjustment, patients with left-sided tumors had superior survival with chemotherapy (HR 0.85,  $p < 0.001$ ) and no difference in survival without chemotherapy (HR 0.97,  $p = 0.18$ ).

**Conclusions** The side of the primary tumor impacts overall survival across stages for colon adenocarcinoma. Patients with right-sided tumors have superior survival for stage I–II disease while patients with left-sided stage III disease demonstrate a survival advantage, suggesting an opportunity for investigators to use sidedness as a surrogate for prognosis and chemoresponsiveness.

**Keywords** Colon adenocarcinoma · Overall survival · Sidedness · Left versus right · Chemotherapy · Surgery

## Introduction

Colorectal cancer is a leading cause of cancer deaths in developed countries. While improvements in early detection through screening programs with endoscopy and fecal occult blood testing have decreased the incidence of death from colorectal malignancies, patients continue to present with advanced disease [1]. Despite progress in detection and systemic and targeted therapies, patients with colon adenocarcinomas of all stages continue to die of their disease.

Multiple studies report biologic and survival differences between right- and left-sided primary colorectal tumors across all stages [2]. Patients with right-sided malignancies are reported to have decreased survival in stage III and IV

disease [3–5]. As a group, patients with right-sided tumors present with older age at diagnosis, more advanced tumor at diagnosis, more aggressive histology at diagnosis, and more females than left-sided tumors [6–9], with the exception of some studies of stage II disease [9–11]. In a recent meta-analysis, left-sided primary tumors were associated with a significantly reduced risk of death, independent of stage, race, or adjuvant chemotherapy [12]. The behavior differences between right- and left-sided diseases may not be surprising given the different embryologic origin and different vascular anatomy of the right and left colon. Furthermore, gene expression is different in the midgut and hindgut portions of the colon, attributed to both embryologic and environmental factors [13–17]. While tumor sidedness is increasingly implicated as a prognostic factor, it is not currently accounted for in staging, prognosis, or treatment.

Despite increasing knowledge regarding the impact of right compared to left-sided colon adenocarcinoma, the available literature is limited to data from highly selective clinical trials and does not represent a broad, practice-based, population study. The aim of this study was to evaluate the

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impact of left compared to right-sided primary tumors on overall survival for patients at each stage of colon cancer utilizing a large representative national database.

## Materials and methods

The National Cancer Database (NCDB) is a clinical surveillance database for the United States. It was developed in conjunction with the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. Over 70% of new cancer diagnoses in the United States are captured through data collection from CoC accredited cancer care centers. The data are culled from medical records by cancer registrars using the CoC Registry Operations and Data Standards Manual, the American Joint Committee for Cancer Manual for Staging of Cancer, and the International Classification of Diseases for Oncology, Third Edition (ICD-O3) [18].

Demographic, oncologic, and institutional variables were extracted from the NCDB 2006–2013 participant user file including patient age, gender, race, annual income, education status, insurance type and status, year of diagnosis, comorbidities, geographic location and type of the treating hospital, histologic diagnosis, pathologic stage of tumor, tumor grade, extent of resection, and receipt of chemotherapy [19]. Education level and income were extrapolated from the median of those values based on the patient's zip code. Comorbidity distinctions are provided as Charlson–Deyo scores [20]. Hospital types are categorized through the NCDB as community (accession 100–500 new cancer cases per year), comprehensive community (accession greater than 500 new cancer cases per year), or academic centers (accession greater than 500 new cancer cases per year, provide postgraduate medical education, research, and clinical trials).

The primary outcome of overall survival was compared for resected stage I–III colon adenocarcinoma sub-grouped by sidedness of the primary tumor. Patients who died within 30 days of resection were excluded to minimize the impact of perioperative morbidity on survival. Sidedness of the primary tumor was determined by the Surveillance Epidemiology and End Results Program (SEER) ICC-O-3 site codes [21] as follows: right sidedness was defined as resection from cecum through transverse colon, and left sided was the splenic flexure to the rectosigmoid. Rectosigmoid tumors, as determined by NDCB coders were excluded. Consistent with other large studies of colon cancer, rectal tumors were excluded allowing comparisons across papers while still leveraging the benefits of our large dataset [10]. Furthermore, it allowed for more direct comparison given the difference in treatment algorithms for colon versus rectal cancers by stage and location. We reviewed the postoperative outcomes

of length of stay, readmission, 30-day mortality, and oncologic outcomes including extent of resection, total number of lymph nodes harvested, and postoperative chemotherapy of right-sided compared to left-sided primary tumors.

## Statistical analysis

To analyze the impact of sidedness on overall survival, Cox proportional hazard modeling was performed while adjusting for patient (age, gender, race, insurance coverage, income, education, and comorbidities), operative (extent of operation, resection of contiguous organ, lymph node harvest, and length of stay), tumor (primary tumor site, tumor and node staging, pathologic staging, and level of differentiation), and facility characteristics (year of operation, academic vs. comprehensive community vs. community hospital). All statistical tests were two tailed with a significance level considered to be  $p < 0.05$  and were performed using R Version 3.4.0 (Vienna, Austria).

## Results

### Stage I–III colon adenocarcinoma, unadjusted

For stages I–III, 198,510 patients were identified. Of those, 78,533 had left-sided tumors and 119,977 had right-sided tumors. In unadjusted analysis, median age at resection was younger for those with left-sided (64 years, interquartile range (IQR): 54–74 years) compared to right-sided tumors (71 years, IQR: 61–80 years,  $p < 0.001$ ). Those with left-sided tumors were more likely to be male (52.7% vs. 44.1%,  $p < 0.001$ ), non-white race (17.6% vs. 15.8%,  $p < 0.001$ ), have fewer comorbidities (Charlson–Deyo score = 0, 72.3% vs. 66.9%,  $p < 0.001$ ), and be privately insured (44.0% vs. 31.5%,  $p < 0.001$ ). Small, but statistically significant, differences were seen in tumor size, cellular differentiation, microsatellite instability, KRAS mutation, and perineural and lymphovascular invasion (all  $p < 0.001$ ), although there was substantial proportion of data reported as “No/Unknown” and these could not be separated to know the proportion of missing data in these fields. Left-sided tumors were more often T1 (17.0% vs. 12.8%,  $p < 0.001$ ), N1 (26.1% vs. 22.5%,  $p < 0.001$ ), stage III (39.6% vs. 36.4%,  $p < 0.001$ ), more likely to have segmental colectomy (66.2% vs 19.2%,  $p < 0.001$ ) and elective resection (77.5% vs. 75.6%,  $p < 0.001$ ), but more often had positive margins (5.1% vs. 4.7%,  $p < 0.001$ ). Median overall length of stay was equivalent between sides (6 days,  $p = 0.203$ ). Patients with left-sided tumors were more likely to receive adjuvant chemotherapy (38.7% vs. 31.3%,  $p < 0.001$ ) (Table 1). Those who died within 30 days of resection were excluded for the local stages.

**Table 1** Stage I–III unadjusted summary of characteristics

	Right (cecum-transverse) ( <i>N</i> = 119,977)	Left (splenic flexure-sig- moid) ( <i>N</i> = 78,533)	<i>p</i> value
Age, years median (lower quartile–upper quartile)	71 (61–80)	64 (54–74)	<0.001
Gender			<0.001
Male	44.1% (52,957)	52.7% (41,375)	
Female	55.9% (67,020)	47.3% (37,158)	
Race			<0.001
White	84.1% (100,027)	82.4% (64,077)	
Black	12.8% (15,242)	12.4% (9622)	
Other	3.0% (3599)	5.2% (4037)	
Charlson–Deyo comorbidity index			<0.001
0	66.9% (80,239)	72.3% (56,818)	
1	23.7% (28,448)	20.8% (16,321)	
2+	9.4% (11,290)	6.9% (5394)	
Facility type			<0.001
Community	16.4% (17,976)	16.6% (11,654)	
Comprehensive	56.8% (62,076)	55.7% (39,120)	
Academic	26.8% (29,270)	27.8% (19,515)	
Insurance status			<0.001
Uninsured	2.8% (3269)	4.0% (3130)	
Private	31.5% (37,304)	44.0% (34,135)	
Government	65.8% (77,918)	51.9% (40,262)	
Income level			0.004
Below median	31.5% (36,475)	32.1% (24,322)	
Above median	68.5% (79,462)	67.9% (51,493)	
Education level			<0.001
Below median	40.0% (46,355)	42.2% (31,988)	
Above median	60.0% (69,575)	57.8% (43,814)	
Year of diagnosis			<0.001
2006	13.7% (16,447)	14.4% (11,307)	
2007	14.3% (17,191)	14.8% (11,589)	
2008	14.5% (17,365)	14.7% (11,547)	
2009	14.2% (17,055)	14.1% (11,040)	
2010	14.4% (17,224)	13.9% (10,922)	
2011	14.4% (17,311)	14.1% (11,058)	
2012	14.5% (17,384)	14.1% (11,070)	
Tumor size			<0.001
< 1 cm	4.4% (4991)	4.9% (3474)	
1–1.9 cm	7.2% (8179)	9.1% (6458)	
2–4.9 cm	48.0% (54,523)	52.7% (37,271)	
> 4.9 cm	40.4% (45,847)	33.2% (23,476)	
Tumor grade			<0.001
Well to moderately differentiated	77.5% (89,776)	87.1% (65,051)	
Poorly or undifferentiated	22.5% (26,075)	12.9% (9674)	
Microsatellite instability			<0.001
No/unknown	97.0% (116,424)	98.5% (77,358)	
Yes	3.0% (3553)	1.5% (1175)	
KRAS mutation			<0.001
No/unknown	98.3% (117,996)	98.7% (77,524)	
Yes	1.7% (1981)	1.3% (1009)	

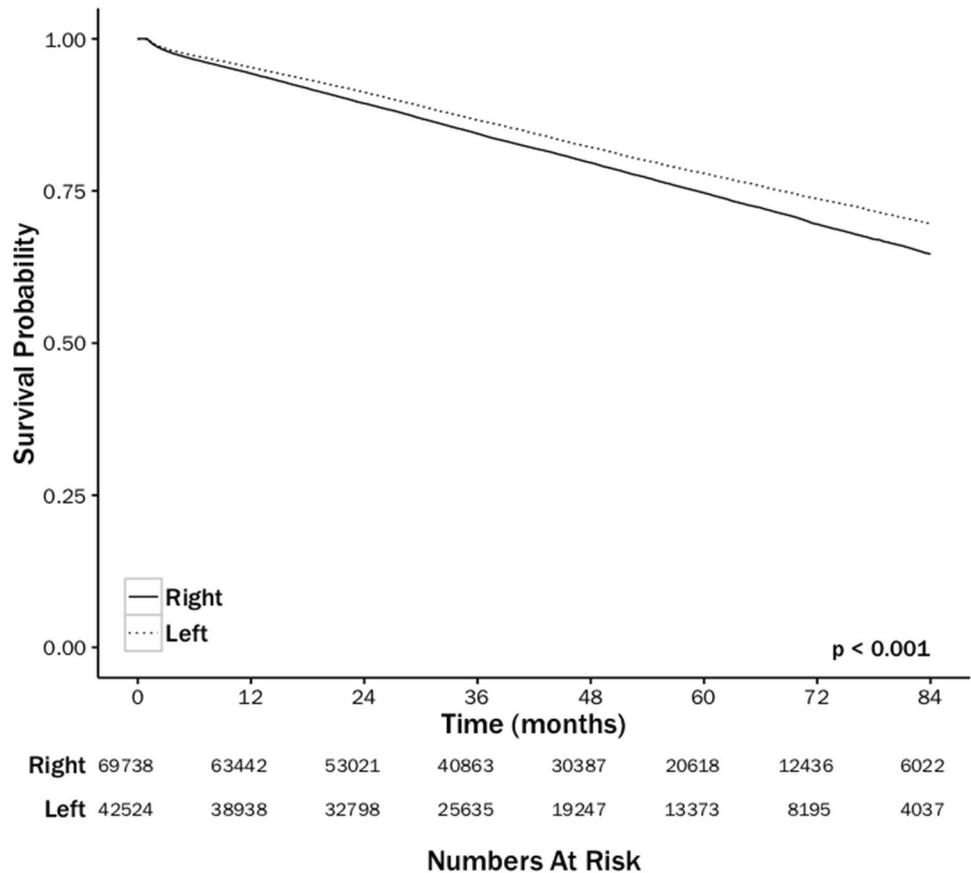
Table 1 (continued)

	Right (cecum-transverse) (N= 119,977)	Left (splenic flexure-sig- moid) (N= 78,533)	p value
18q loss of heterozygosity			0.063
No/unknown	99.9% (119,890)	99.9% (78,493)	
Yes	0.1% (87)	0.1% (40)	
Carcinoembryonic antigen			0.134
No/unknown	79.8% (95,781)	79.6% (62,478)	
Yes	20.2% (24,196)	20.4% (16,055)	
Perineural invasion			<0.001
No/unknown	96.2% (115,406)	95.7% (75,155)	
Yes	3.8% (4571)	4.3% (3378)	
Lymphovascular invasion			<0.001
No/unknown	89.3% (107,098)	90.0% (70,697)	
Yes	10.7% (12,879)	10.0% (7836)	
Pathologic T stage			<0.001
T0/is	1.4% (1562)	1.7% (1300)	
T1	12.8% (14,701)	17.0% (12,658)	
T2	17.5% (20,125)	15.5% (11,525)	
T3	57.0% (65,566)	54.5% (40,573)	
T4	11.4% (13,077)	11.3% (8437)	
Pathologic N Stage			<0.001
N0	63.7% (73,099)	60.6% (45,131)	
N1	22.5% (25,871)	26.1% (19,419)	
N2	13.8% (15,840)	13.3% (9894)	
Disease stage			<0.001
Stage 0	1.3% (1472)	1.6% (1188)	
Stage I	26.1% (29,874)	26.2% (19,430)	
Stage II	36.2% (41,440)	32.5% (24,095)	
Stage III	36.4% (41,711)	39.6% (29,313)	
Extent of colectomy			<0.001
Segmental	19.2% (23,072)	66.2% (51,983)	
Hemicolectomy/total	80.8% (96,905)	33.8% (26,550)	
Resection of contiguous organ			<0.001
No	94.0% (112,749)	94.6% (74,316)	
Yes	6.0% (7228)	5.4% (4217)	
Emergency surgery status			<0.001
Elective	75.6% (88,775)	77.5% (59,475)	
Emergent	24.4% (28,707)	22.5% (17,295)	
Lymph nodes examined median (lower quartile– upper quartile)	18 (13–24)	15 (11–21)	<0.001
Surgical margins			<0.001
Negative	95.3% (113,315)	94.9% (73,743)	
Positive	4.7% (5553)	5.1% (3924)	
Hospital length of stay (days)	4/6/8	4/6/8	0.203
30-day unplanned readmission			<0.001
No	94.5% (110,567)	95.0% (72,691)	
Yes	5.5% (6463)	5.0% (3840)	
30-day mortality			
No	100% (119,977)	100% (78,533)	
Yes	0% (0)	0% (0)	

**Table 1** (continued)

	Right (cecum-transverse) (N=119,977)	Left (splenic flexure-sigmoid) (N=78,533)	<i>p</i> value
Postoperative chemotherapy			<0.001
No	68.7% (80,282)	61.3% (46,918)	
Yes	31.3% (36,502)	38.7% (29,656)	

**Fig. 1** Kaplan–Meier curve for unadjusted survival, stage I–II by sidedness of tumor



**Adjusted survival: stage I–II**

Survival was calculated separately for stages I–II and stage III. For stages I–II, patients with left-sided tumors had better survival than those with right-sided tumors ( $p < 0.001$ ) (Fig. 1). However, after adjustment, the results were reversed: patients with right-sided tumors survived

longer than those with left-sided tumors [hazard ratio (HR) 1.13, 95% CI 1.09–1.17,  $p < 0.001$ ] (Table 2).

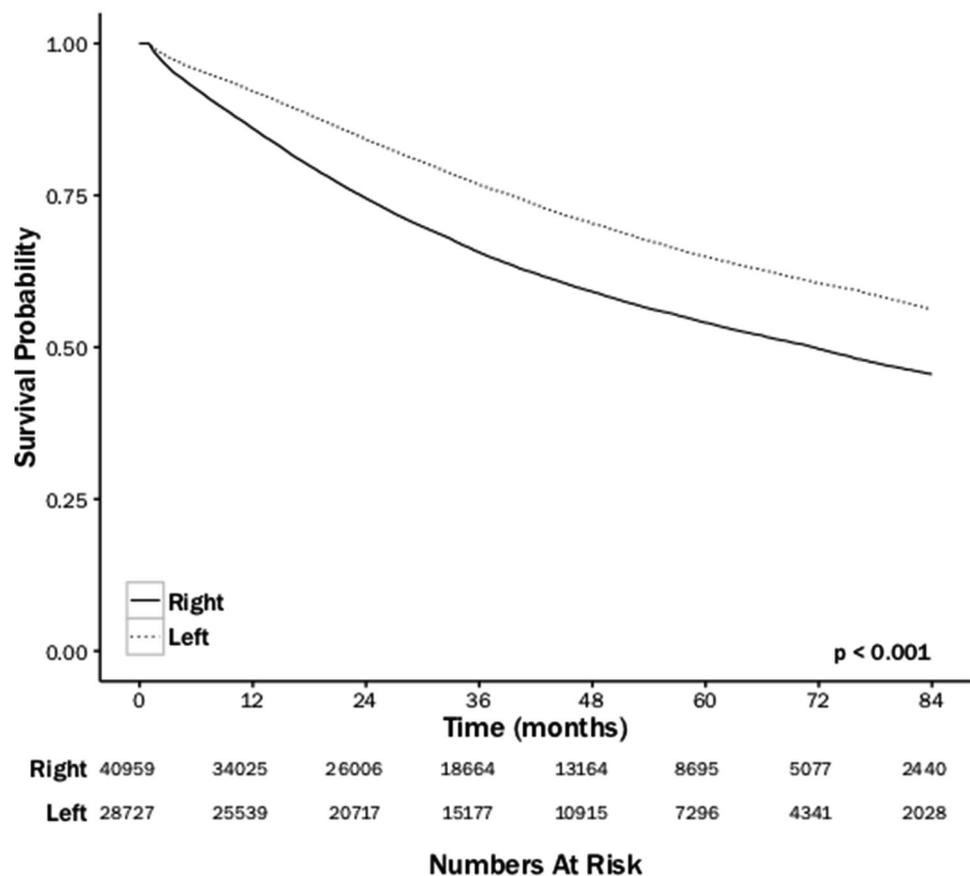
**Adjusted survival: stage III**

For stage III, patients had improved survival with left-sided tumors compared to right-sided tumors ( $p < 0.001$ ) (Fig. 2). Adjusted analysis was performed by receipt of

**Table 2** Summary table of adjusted hazards of death with left-sided primary tumors as the reference value

Stage	Survival by side	Hazard ratio (95% confidence interval)	<i>p</i> value
Stage I–II	Right > left	1.13 (1.09–1.17)	<0.001
Stage III without chemotherapy	Left > right	0.97 (0.912–1.02)	0.18
Stage III with chemotherapy	Left > right	0.85 (0.815–0.892)	<0.001

**Fig. 2** Kaplan–Meier curve for unadjusted survival, stage III by sidedness of tumor



chemotherapy. Patients with stage III tumors who did not receive chemotherapy had no difference in overall survival between right- and left-sided primaries (HR 0.97, CI 0.92–1.02,  $p=0.18$ ). However, for patients who had chemotherapy, patients with left-sided tumors had improved survival compared to those with right-sided primaries (HR 0.85, CI 0.82–0.89,  $p<0.001$ ) (Table 2).

## Discussion

In this analysis, sidedness of the primary tumor in colonic adenocarcinoma has a significant impact on overall survival in both unadjusted and adjusted analysis. For stage I–II tumors, patients with right-sided primaries have superior survival compared to those with left-sided primaries after adjustment. For stage III, patients with left-sided primaries who receive chemotherapy have superior survival compared to those with right-sided primaries, with no impact of sidedness for patients who did not receive chemotherapy (Table 2). Our results are consistent with conclusions from recent institutional studies, clinical trials, and SEER data [3]. To date, this NCDB cohort provides the largest and most inclusive patient population examined, making this study

uniquely applicable to a broad range of colorectal cancer patients.

For stage I–II disease, our analysis suggests superior overall survival for patients with right-sided primaries compared to left-sided tumors. These conclusions are drawn from the largest cohort of patients examined in the literature thus far. Our findings are supported by prior studies including a SEER analysis [10, 11], the Australian Cancer Registry [9], and the German Colon/Rectum Cancer Study [22], but differ from the null results of the study of stage I–III tumors from Ontario [23]. The etiology of these discordant findings is likely multifactorial, related to both surveillance colonoscopy and tumor biology [2, 10, 17, 24, 25]. Baxter et al. [26] identified a left, but not right-sided survival advantage related to endoscopic screening which could account for a left-sided survival advantage in early-stage disease. Conversely, the findings by Baker and colleagues suggest a more favorable right-sided biology in early disease as right-sided lesions were associated with dysregulated growth, where left-sided lesions were associated with changes in cellular differentiation [27]. Additionally, right-sided lesions are associated with the presence of greater microsatellite instability. While our analysis was limited by missing data of specific markers (microsatellite instability and KRAS) the findings by Baker and colleagues are supported in our study

as well (right vs left tumors exhibiting 3.0% vs 1.5% rate of microsatellite instability, respectively,  $p < 0.001$ ), and these tumors are associated with a favorable prognosis [2, 10, 17, 24, 25].

In stage III tumors, our analysis demonstrated survival advantage in patients with left-sided tumors, also congruent with prior findings [6, 11, 12, 22]. This survival advantage appears to be specific to patients who received chemotherapy for stage III tumors. While chemotherapy is a recorded variable for select patients with stage II tumors, and this was adjusted for in multivariable analysis, it was such a low percentage of the total that it does not drive the effect size for stage I and II tumors. It is postulated that differential gene expression in the proximal and distal colon [2, 14, 15], is a downstream effect of both developmental factors and differing environmental exposures which may account for variable chemoresponsiveness. Von Einem [7] and colleagues considered wild-type KRAS with respect to tumor location and demonstrated a left-side survival advantage for advanced disease treated with cetuximab in addition to standard chemotherapy (HR 0.67,  $p = 0.02$ ). Our findings build on this concept that left-sided disease has improved survival as this was demonstrated in our stage III analysis without separating patients based on their KRAS status as a limitation of current large-scale data collection does not include these markers. While all patients with stage III tumors have adjuvant chemotherapy recommended [28], a higher percentage of patients with left-sided tumors completed the treatment (20% vs 18%,  $p < 0.001$ ) [11]. Completion of adjuvant therapy was independently associated with improved survival (HR 0.59,  $p < 0.001$ ) [11]. However, receipt of chemotherapy incompletely describes this survival difference as tumor responsiveness to chemotherapy by side has not been determined.

Limitations to our study are those inherent to retrospective analyses of large clinical databases with the possibility of coding errors; however, the data collection process for the NCDB is well standardized, and data reporting is closely audited [18]. Possible confounding exists for clinical factors not captured within the dataset. The dose, type, and completion of chemotherapeutic regimens are not included in the NCDB. Performance status, and postoperative complications are not available for analysis, but surrogates of Charlson–Deyo comorbidity index, length of stay and readmission are accepted as appropriate surrogates. Tumor markers are not always tested for, and our data are limited by the combination of negative results and missing data. Additionally, survival is only reported as overall survival, not disease-specific survival, making direct comparisons with prospective trials that report disease-specific survival challenging. Finally, to allow for comparison with other smaller institutional studies and to ensure optimal

usage of a large dataset, we chose to limit our analysis to colon cancers as defined by anatomical location. We recognize that as research matures our understanding of the biological underpinnings of the various colorectal cancers, this analysis will have to be refined in way that will more precisely group various colorectal cancers, perhaps even including rectal cancers in the analysis. Currently, biological markers are neither understood well enough nor captured in the NCDB to justify using them in lieu of anatomical location. The strength of our study lies in the large sample size of the national dataset permitting for adequate adjustment for confounding factors for survival including annual income, geographic location, hospital types, and clinico-pathologic factors despite the limitation of granularity in the data accumulated. The NCDB has an advantage over SEER data in its inclusion of patients less than 65 years old and it captures 70% of new cancer diagnoses compared to 26% of cancer cases captured in SEER [19]. The inclusion of all stage I–III colon adenocarcinoma patients captured in the NCDB 2006–2013 is reflective of contemporary management patterns of the United States patient population.

## Conclusions

Our results demonstrate that the side of the colon in which a primary tumor occurs has an impact on overall survival for colonic adenocarcinoma stages I to III. Early-stage disease (I–II) demonstrates a survival advantage for right-sided tumors while stage III disease portends improved survival in left-sided tumors, specifically following receipt of chemotherapy. These data support ongoing efforts to better understand the biologic underpinnings of these findings as a powerful strategy to better predict prognosis and select therapies for patients with colorectal cancer.

**Author contributions** All the authors have approved the final manuscript. MCT was responsible for concept generation, data acquisition, statistical analysis, data interpretation, manuscript writing, revisions and submission. DB was responsible for data interpretation, manuscript writing, and manuscript revisions. ZS was responsible for concept generation, data acquisition, statistical analysis, data interpretation, and manuscript revisions. KL was responsible for concept generation, data interpretation, and manuscript revisions. JW was responsible for data interpretation, manuscript writing, revisions and submission. JM was responsible for concept generation, data acquisition, data interpretation, and manuscript revisions. CRM was responsible for concept generation, data acquisition, data interpretation, and manuscript revisions. DGB was responsible for concept generation, data interpretation, and manuscript revisions and provided study oversight.

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## Compliance with ethical standards

**Conflict of interest** The authors declare no conflicts of interest.

**Ethics approval and consent to participate** This study was granted exempt status by the Duke Institutional Review Board given the de-identified nature of the dataset.

**Informed consent** Informed consent was not performed in this setting.

**Availability of the data and material** The data were acquired by application through the National Cancer Database (NCDB). The statistical analysis was performed in R (Vienna, Austria). The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. The data used in this study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigators.

## References

- Edwards BK, Ward E, Kohler BA, Eheman C, Zauberg AG, Anderson RN et al (2010) Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. *Cancer* 116(3):544–573
- Gervaz P, Bucher P, Morel P (2004) Two colons-two cancers: paradigm shift and clinical implications. *J Surg Oncol* 88(4):261–266
- Ciombor KK, Goldberg RM (2017) Primary tumor sidedness as prognostic and predictive biomarker in metastatic colorectal cancer: further validation of a potentially practice-changing variable. *JAMA Oncol* 3(2):165–166. <https://doi.org/10.1001/jamaoncol.2016.3777>
- Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Sonesson C, Budinska E et al (2014) Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann Oncol* 25(10):1995–2001
- Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F et al (2017) Prognostic and predictive relevance of primary tumor location in patients with ras wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. *JAMA Oncol* 3(2):194–201. <https://doi.org/10.1001/jamaoncol.2016.3797>
- Price TJ, Beeke C, Ullah S, Padbury R, Maddern G, Roder D et al (2015) Does the primary site of colorectal cancer impact outcomes for patients with metastatic disease? *Cancer* 121(6):830–835
- von Einem JC, Heinemann V, von Weikersthal LF, Vehling-Kaiser U, Stauch M, Hass HG et al (2014) Left-sided primary tumors are associated with favorable prognosis in patients with KRAS codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KKR-0104 trial. *J Cancer Res Clin Oncol* 140(9):1607–1614
- Hansen IO, Jess P (2012) Possible better long-term survival in left versus right-sided colon cancer—a systematic review. *Dan Med J* 59(6):A4444
- Brungs D, Aghmesheh M, de Souza P, Ng W, Chua W, Carolan M, Clingan P, Healey E, Rose J, Tubaro T, Ranson M (2017) Sidedness is prognostic in locoregional colon cancer: an analysis of 9509 Australian patients. *BMC Cancer* 17(1):251. <https://doi.org/10.1186/s12885-017-3255-z>
- Meguid RA, Slidell MB, Wolfgang CL, Chang DC, Ahuja N (2008) Is there a difference in survival between right- versus left-sided colon cancers? *Ann Surg Oncol* 15(9):2388–2394
- Weiss JM, Pfau PR, O'Connor ES, King J, LoConte N, Kennedy G et al (2011) Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results—Medicare data. *J Clin Oncol* 29(33):4401–4409
- Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dalleria P et al (2017) Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol* 3(2):211–219. <https://doi.org/10.1001/jamaoncol.2016.4227>
- Nasir A, Lopez A, Boulware D, Malafa M, Coppola D (2011) Correlation between COX-2 and APC expression in left versus right-sided human colon cancer. *Anticancer Res* 31(6):2191–2195
- Birkenkamp-Demtroder K, Olesen SH, Sorensen FB, Laurberg S, Laiho P, Aaltonen LA et al (2005) Differential gene expression in colon cancer of the caecum versus the sigmoid and rectosigmoid. *Gut* 54(3):374–384
- Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ et al (2003) Distinguishing right from left colon by the pattern of gene expression. *Cancer Epidemiol Biomarkers Prev* 12(8):755–762
- Brule SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R et al (2015) Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. *Eur J Cancer* 51(11):1405–1414
- Lee MS, Menter DG, Kopetz S (2017) Right versus left colon cancer biology: integrating the consensus molecular subtypes. *J Natl Compr Cancer Netw* 15(3):411–419
- Winchester DP, Stewart AK, Phillips JL, Ward EE (2010) The national cancer data base: past, present, and future. *Ann Surg Oncol* 17(1):4–7
- <http://ncdbpub.facs.org/>
- Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 45(6):613–619
- National Cancer Institute (US), SEER Program (National Cancer Institute (US)). Surveillance, epidemiology, and end results [unspecified]. Bethesda, Md.: The Institute. <http://seer.cancer.gov/>. Accessed Jan 2018
- Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H et al (2010) Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. *Dis Colon Rectum* 53(1):57–64
- Karim S, Brennan K, Nanji S, Berry SR, Booth CM (2017) Association between prognosis and tumor laterality in early-stage colon cancer. *JAMA Oncol* 3(10):1386–1392
- Popat S, Hubner R, Houlston RS (2005) Systematic review of microsatellite instability and colorectal cancer prognosis. *J Clin Oncol* 23(3):609–618
- Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM et al (2003) Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 349(3):247–257
- Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L (2009) Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 150(1):1–8
- Baker K, Zhang Y, Jin C, Jass JR (2004) Proximal versus distal hyperplastic polyps of the colorectum: different lesions or a biological spectrum? *J Clin Pathol* 57(10):1089–1093
- National Comprehensive Cancer Network (US) (2003) The complete library of NCCN clinical practice guidelines in oncology. Rockledge, PA: National Comprehensive Cancer Network. [http://www.nccn.org/professionals/physician\\_gls/default.asp](http://www.nccn.org/professionals/physician_gls/default.asp). Accessed Nov 2016

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