Published in final edited form as:

Surgery. 2014 August ; 156(2): 305–310. doi:10.1016/j.surg.2014.03.036.

A Comparison of Colorectal Cancer in West African and North American Patients: Is the Cancer Biology Different?

Saurabh Saluja, MD, Olusegun I Alatise, MD, Adisa Adewale, MD, Justine Misholy, BA, Joanne Chou, MPH, Mithat Gonen, PhD, Martin Weiser, MD, and T. Peter Kingham, MD

Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, USA Department of Surgery, Obafemi Awolowo University, Ile-Ife, Nigeria

Abstract

Background—70% of the 24 million people predicted to have cancer by 2050 will live in low- and middle-income countries (LMIC). As a result, cancer care is becoming a priority for healthcare systems in West Africa. This study compares the presentation and pattern of spread of colorectal cancer (CRC) observed in a hospital in West Africa (Nigeria) to that of a North American referral center (New York City).

Methods—Data on all adults presenting with CRC at a hospital in West Africa (Nigeria; 1990-2011) and all adults with stages III or IV CRC at a specialty hospital in North America (New York City; 2005-2011) were retrospectively examined. Demographic data, stage of disease, site of metastasis, and survival were compared.

Results—There were 160 patients identified in West Africa and 1,947 patients identified in North America. West African patients were younger (52 vs 59 years, $p < 0.01$) and presented with a later stage of disease (58% stage IV versus 47%, $p < 0.01$). Site of disease presentation was significantly different between West African and North American patients ($p < 0.01$). 2.2% of West African patients presented with liver metastases only, compared to 48.1% of North American patients. Conversely, 61.3% of patients in West Africa presented with peritoneal metastases only, compared to 5.4% in North America. OS stratified by stage at presentation (III/IV) showed worse prognosis for patients in either stage subgroup in Nigeria than North America.

Conclusion—We found differences in the presentation, metastatic pattern, and outcomes of CRC in West Africa when compared to North America. Late detection and differential tumor biology may drive the differences observed between the sites. Future studies on early CRC detection and on tumor biology in LMIC will be critical for understanding and treating CRC in this region.

Corresponding Author: T. Peter Kingham, MD, 1275 York Ave, C-886, Memorial Sloan Kettering Cancer Center, Work: 212-639-5260, Alternative ph: 212-794-5852, kinghamt@mskcc.org, Fax: 212-794-5852.

*Presented at the 9th Annual Academic Surgical Congress in San Diego, CA, Feb. 4-6, 2014

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Keywords

Colorectal cancer; Outcomes data; West Africa; Screening; Global Health; Tumor Biology

Introduction

Cancer is a leading cause of death worldwide and in 2008 accounted for 13% of all mortality.¹ While the incidence of cancer is highest in Europe and the Americas, low and middle-income countries (LMIC) also suffer an appreciable burden of disease. As population demographics change, new cancer diagnoses are expected to exceed 20 million per year by 2030, with nearly two-thirds of these diagnoses occurring in LMIC.²

The cancers that exert the greatest burden of disease are primarily solid tumors¹ for which surgical resection is a major component of treatment. As high-income countries have appreciated a decreasing incidence and increasing survival for most of these cancers, many LMIC are observing the opposite.³⁻⁵ Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide⁴ and rising rates have been observed in LMIC.⁵⁻⁸ There is a need to examine the etiology, presentation, biology and outcomes of CRC in LMIC and how it may differ from CRC in better-studied parts of the world.

In this study, we compare the presentation and pattern of spread of CRC observed in a hospital in West Africa (Nigeria) to a North American (New York City) referral center. Examining the differences between West African and North American CRC may help us understand the variable clinical course that this cancer can take, raise further questions as to the tumor biology that underlies CRC, and may ultimately have implications for treating CRC in West Africa and amongst West African immigrant populations.

Methods

In West Africa, data were obtained from a Nigerian hospital, Obafemi Awolowo University Hospital (OAU). OAU is a tertiary referral hospital with a catchment area of 25 million patients. The charts of all patients diagnosed with CRC between 1990 and 2011 were reviewed by one of the study authors (OIA). Patients without a medical chart present at the time of data collection were excluded. In North America, data were obtained from a prospectively maintained database of all CRC patients treated at a specialty cancer hospital (Memorial Sloan Kettering Cancer Center, MSKCC). These data were crosschecked with a prospectively maintained database of all CRC patients presenting with liver metastases. Patients in this population were included if they presented with or developed a diagnosis of Stage III or IV CRC between 2005 and 2011 and were over age 18. Survival data reflects time from date of diagnosis to death or loss to follow-up. In both sites, follow-up data were limited to patients who continued to seek care at the study hospital. OAU and MSKCC have started an NCI recognized consortium (The African coloRectal cancer GrOup; ARGO) to prospectively build a database and biobank to study colorectal cancer in Nigeria.

In West Africa, staging was performed by physical exam (e.g size of rectal masses, palpable liver lesions), abdominal ultrasound, chest x-ray and laparotomy. In a select group of patients treated in recent years, colonoscopy, diagnostic laparoscopy or CT scan may also have been performed. In the US, staging modalities included physical exam, colonoscopy, endorectal ultrasound, CT scan, MRI and PET scan.

Statistical Methods

Patient demographic data, disease, tumor, and treatment characteristics were compared using Chi-square test for categorical variables or Wilcoxon Rank Sum test for continuous variables. Fisher exact test was used to compare the association between site of metastases to the liver and whether patients presented with obstruction among stage IV patients. Overall survival (OS) was calculated from date of diagnosis/surgery until the time of death. Patients who did not experience the event of interest by the end of the study were censored at the time of the last available follow-up. OS was estimated using the Kaplan-Meier method and the survival probabilities between patients in the two regions were compared using log-rank test.

Time to first recurrence was estimated by cumulative incidence function. The main event of interest was peritoneum recurrence without liver involvement. Stage III patients who had a liver recurrence without peritoneum involvement (N=106), both peritoneum and liver recurrence (N=11), other recurrence without involvement to either liver or peritoneum (N=61) or died without a recurrence (N=52) were considered as competing events. Gray's test⁹ was used to test the difference in time to recurrence between the two countries. All P values were based on 2-tailed statistical analysis. All analyses were performed with SAS version 9.3 (SAS institute, Cary, North Carolina) and R (version 10.2).

Results

There were 160 patients identified at the West African center and 1,947 patients identified at the North American center. Patients in West Africa were significantly younger (52 vs 59 years, $p<0.01$) and more commonly male (61% vs 52%, $p<0.01$) (Table 1). Seven percent of North American patients were African American. In the West African dataset, 144 of the patients had complete data describing which surgical procedure was performed. In the North American dataset, 1,657 patients had complete data describing which surgical procedure was performed. West African patients more commonly presented with rectal primary tumors (53% vs 32.3%, $p<0.01$) and had a bowel obstruction as a presenting symptom (45% vs 28%, $p<0.01$). In West Africa, 41% of patients presented with stage III disease and 58% presented with stage IV disease, whereas in North America, where the study population was limited to stage III and IV disease, the population was nearly evenly divided between stages. 49 (2.5%) patients in North America entered the study period with stage II cancer and subsequently developed metastases whereas one patient in West Africa entered the study period with stage I cancer and developed metastases.

A similar percentage of patients received neoadjuvant and adjuvant chemotherapy at both sites (Table 2). There was a significant difference in the treatment of rectal cancers with neoadjuvant radiation therapy ($p<0.01$). In patients that presented with Stage III rectal

cancer (N=442), in Nigeria 4.4% (n=1) had neoadjuvant radiotherapy, compared to 82% (n=342) in North America. The most commonly performed procedure was a diverting colostomy in the West African center and an extended right hemi-colectomy in the North American center. The treatment of patients with liver metastases (N=756) was different between both institutions. In Nigeria, none of the 18 patients that presented with liver metastases had a liver resection, compared to 55.9% (n=413) of patients that presented with liver metastases in the tertiary referral cancer center in North America.

The metastatic pattern was significantly different between the two centers ($p<0.01$). Amongst stage IV patients, 2.2% of West African patients presented with liver metastases only, 61.3% presented with peritoneum only, 10.7% presented with both liver/peritoneum only, and 25.8% presented with metastases elsewhere. In contrast, 48.1% of North American patients presented with liver disease only, 5.4% presented with peritoneum only, 4.6% presented in both liver and peritoneum, and 41.8% presented elsewhere (Table 3). Among Stage III CRC patients who did not present with metastases, the cumulative incidence of developing peritoneal disease without liver involvement 2 years from surgery was 16.3% in West Africa and 2% in North America (Table 3, $p<0.01$). In stage IV patients that presented with obstruction (N=388), 84.1% (n=287/341) of patients in North America had concomitant liver metastases, compared to 8.3% (n=6/47) in Nigerian patients ($p<0.01$).

Survival data were available for all of the North American patients and 137 of the West African patients. Median follow-up period amongst survivors was three years at both centers. Both overall survival (35% vs 67%) (Figure 1) and survival stratified by stage at presentation (Stage III 62% vs 88%, stage IV 10% vs 45%) (Figure 2) was significantly lower in West Africa than in North America. Two-year overall survival in stage IV patients with peritoneal only disease was 25% in West Africa (95% CI: 12%-40%) and 60% in North America (95% CI: 43-72%, $p<0.01$). The small number of West African patients with liver metastases precluded an analysis of their survival.

Discussion

An increasing rate of CRC has been observed in many LMI,⁵ including in West Africa.⁶⁻⁸ In Nigeria, Ibrahim et al. found that 40% of all CRC cases observed in a 30-year period occurred in the final five years of the study (2004-2008). Meanwhile the surgical biopsy registry at Lagos University Teaching Hospital has identified CRC as the third most commonly diagnosed malignancy.⁷ While CRC rates in West Africa are less than those observed in high-income countries, it is increasingly clear that this disease exerts a substantial burden in the region.

There is speculation that changing dietary habits and increasing tobacco use have driven the increasing rate of CRC in the region.^{6-8,10} Further, improvements in access to care may also be leading to a higher rate of CRC detection. However, as CRC rates increase in LMIC, outcomes remain poor. This is thought to be due to late stage of presentation and poor availability of therapy.^{3,11} Despite an increasing understanding of CRC in West Africa, there is no literature to date that directly compares the presentation, outcomes, and metastatic pattern of disease between North America and West Africa. Our results revealed

several differences between the sites. Similar to other authors, we found a higher male-to-female ratio in our West African population.^{7-8,10} This male preponderance may be explained by higher suspected rates of male tobacco use and abdominal obesity^{5,8} or may reflect a selection bias that results from well-documented gender inequity in access to healthcare.¹²

The possibility of different tumor biology is clearest when considering the metastatic pattern observed in the two centers. West African patients were more likely to present with peritoneal disease and less likely to have liver metastases. It is possible this is solely a reflection of advanced primary tumors growing through the wall of the colon and encouraging peritoneal metastases in the West African patients. This is, however, not supported by the significant difference in the percentage of patients with bowel obstruction in West Africa and North America that have liver metastases. These patients are self-selecting in that they present when they have obstructive symptoms, so this group of patients may be the most relevant to compare regarding patterns of metastases. In addition, in West African patients there is a significantly higher rate of patients that present with stage III disease and progress to peritoneal disease as their site of stage IV disease.

One explanation for the difference in metastatic pattern may be the tumor's genetic signature. Liver metastases are caused by hematogenous spread, while peritoneal metastases require detachment of malignant cells, invasion of the peritoneal surface, and successful colonization.¹³ Several studies have compared the biology of primary colon, liver, and peritoneal metastases. Varghese et al. examined 14 liver tumors and 6 peritoneal tumors and found that metastases in these two sites clustered together.¹⁴ Another study examined 18 primary CRC, 4 liver metastases, and 4 peritoneal metastases with DNA microarrays.¹⁵ They concluded that specific genetic signatures were associated with different metastatic sites for CRC.

Differential tumor biology between West Africa and North America has been described in other solid tumors. Breast cancer is more commonly triple-negative amongst indigenous African women¹⁶ and may, as a result, be less responsive to treatments such as tamoxifen. In prostate cancer, genome studies have identified multiple loci for genetic susceptibility to prostate cancer and have found more single nucleotide polymorphisms of the 8q24 locus in West African men than in men of European ancestry.¹⁷

Ethnic genetic differences have also been noted in CRC. African Americans with microsatellite stable and microsatellite low mutation tumors had a higher percentage of KRAS mutations when compared to Caucasians (34% vs. 23%, $p=0.048$).¹⁸ Interestingly, in our study, African Americans behaved more like their North American counterparts than they did like West Africans. If tumor biology is in-fact driving differences between the sites, the genetic link between peritoneal metastases and African ancestry may not be direct.

As is to be expected in an area where CRC screening is scarce, West African patients presented with later stage of disease. In our West African population all of the patients with CRC were found to have stage III or IV disease, whereas in the United States nearly 40% of CRC is diagnosed as stage I disease.¹⁹ In our study, we limited our North American

population to those with stage III or IV CRC, yet even in this population we found that West African patients presented with more advanced disease. This is evident in the higher rate with which West African patients presented with late-stage complications such as bowel obstruction.

In the United States, screening colonoscopy has increased dramatically in the last 20 years,²⁰ leading to detection and removal of precancerous lesions as well as diagnosis of earlier stage disease. Meanwhile, in West Africa, colonoscopy is virtually unavailable as a screening tool. Furthermore, cheaper screening modalities, such as fecal occult blood testing (FOBT), are scarcely used. In a review of CRC in Accra, Ghana, Dakubo and colleagues found rectal bleeding to be the most common symptom, yet patients had an average of 18 months of bleeding before presenting for evaluation.⁶ While rectal bleeding may result from numerous conditions including dysentery or hemorrhoids, educating patients, traditional healers, and health care workers that bleeding may be a harbinger for cancer may be an important first step in improving early detection. FOBT may also have a role for improving CRC detection in LMIC. In a Slovenian study on screening with FOBT, 7.5% of screened patients had a positive test and 7.7% of these patients were diagnosed with invasive carcinoma – most of which were detected as stage I or II disease.²¹ In West Africa, FOBT may similarly prove to be a useful initial screening test.

We also found a substantial difference in survival between the two centers. This may be due to delayed presentation or limited availability of therapy. It is difficult to compare outcomes between both locations due to the large disparity in many aspects of care. In our study, only one West African patient received radiation therapy or a liver resection and the availability of chemotherapy depended on the patients' ability to pay. However, we found that a similar percentage of patients at both sites received chemotherapy, yet the survival disparity persisted even amongst stage-matched patients, raising the question as to whether tumor behavior and response to chemotherapy in West Africa is different from North America. While these questions cannot be answered with these retrospective data, when we compared patients with peritoneal disease or liver disease, the differences persisted. In order to address these questions prospectively, a colorectal cancer consortium has been created in Nigeria.

Our study is limited by its retrospective design. Data on surgical procedure and on specific chemotherapy modalities were not available on all patients in either site. Additionally, staging modalities was not standardized across the sites. The reliance on physical exam in West Africa may, for example, have led to under-detection of liver metastases, or the use of diagnostic laparoscopy may have led to higher rate of detection of peritoneal disease. Access to care at both sites introduces an additional source of bias and CRC in the study populations may not reflect CRC in their respective general populations.

Nevertheless, our data show a marked difference in presentation, stage-matched survival and metastatic pattern of CRC between the two geographic regions. Based on these data, we hypothesize that substantial improvement in CRC outcomes in West Africa could be made by earlier detection. This will require continuing to improve access to care and investing in novel approaches to CRC screening that are suitable for LMIC. In addition, a difference in tumor biology may drive some of the difference in both cancer behavior and outcomes.

Studies to prospectively examine the biologic nature of CRC in West Africa may have implications for treatment similar to what has been found in breast and prostate cancer. This may ultimately change the therapeutic approach to CRC in West Africa.

Acknowledgments

The authors received no funding from outside institutions in carrying out this research. This study was supported in part by NIH/NCI Cancer Center Support Grant P30 CA008748.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: Globocan 2008. *Int J Cancer*. 2010 Dec 15; 127(12):2893–917. [PubMed: 21351269]
2. Alwan, A. Global status report on noncommunicable diseases 2010. Italy: 2010. Chapter 1: Burden, mortality, morbidity and risk factors; p. 9-31.
3. Sankaranarayanan, R.; Swaminathan, R.; Jayant, K.; Brenner, H.; Lucas, E. Cancer survival in Africa, Asia, the Caribbean and Central America (SurvCan). Vol. 162. Lyon: International Agency for Research on Cancer; 2011. An overview of cancer survival in Africa, Asia, the Caribbean and Central America: the case for investment in cancer health services. IARC Scientific Publications
4. Jemal A, Center MM, DeSantis C, Ward M. Global patterns of cancer incidence and mortality rates and trends. *Cancer Epidemiol Biomarkers Prev*. 2010 Aug; 19(8):1893–1907. [PubMed: 20647400]
5. Center MM, Jemal A, Ward E. International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev*. 2009 Jun; 18(6):1688–94. [PubMed: 19505900]
6. Dakubo JC, Naaeder SB, Tettey Y, Gyasi RK. Colorectal carcinoma: an update of current trends in Accra. *West Afr J Med*. 2010 May-Jun; 29(3):178–83. [PubMed: 20665462]
7. Abdulkareem FB, Abudu EK, Awolola NA, Elesha SO, Rotimi O, Akinde OR, et al. Colorectal carcinoma in Lagos and Sagamu, Southwest Nigeria: a histopathological review. *World J Gastroenterol*. 2008 Nov 14; 14(42):6531–5. [PubMed: 19030207]
8. Ibrahim KO, Anjorin AS, Afolayan AE, Badmos KB. Morphology of colorectal carcinoma among Nigerians: a 30-year review. *Niger J Clin Pract*. 2011 Oct-Dec; 14(4):432–5. [PubMed: 22248944]
9. Gray RJ. A class of k-sample tests for comparing the cumulative incidence of a competing risk. *Annals of Statistics*. 1988; 16(3):1141–1154.
10. Sule AZ, Mandong BM, Iya D. Malignant colorectal tumours: a ten year review in Jos, Nigeria. *West Afr J med*. 2001 Oct-Dec; 20(4):251–5. [PubMed: 11885882]
11. Sener SF, Grey N. The global burden of cancer. *J Surg Oncol*. 2005 Oct 1; 92(1):1–3. [PubMed: 16180214]
12. Sen, G.; Ostlin, P.; George, A. Final Report. WHO commission on Social Determinant of Health – Women and Gender Equity Knowledge Network; Sep. 2007 Unequal, unfair, ineffective and inefficient. Gender inequity in health: Why it exists and how we can change it.
13. de Cuba EM, Kwakman R, van Egmond M, Bosch LJ, Bonjer HJ, Meijer GA, et al. Understanding molecular mechanisms in peritoneal dissemination of colorectal cancer: future possibilities for personalised treatment by use of biomarkers. *Virchows Arch*. 2012; 461(3):231–43. [PubMed: 22825001]
14. Varghese S, Burnesss M, Xu H, Beresnev T, Pingpank J, Alexander HR, et al. Site-specific gene expression profiles and novel molecular prognostic factors in patients with lower gastrointestinal adenocarcinoma diffusely metastatic to liver or peritoneum. *Ann Surg Oncol*. 2007; 14(12):3460–71. [PubMed: 17899288]
15. Kleivi K, Lind GE, Diep CB, Melling GI, Brandal LT, Nesland JM, et al. Gene expression profiles of primary colorectal carcinomas, liver metastases, and carcinomatoses. *Mol Cancer*. 2007; 6:2. [PubMed: 17201907]

16. Huo D, Ikpat F, Khramtsov A, Dangou JM, Nanda R, Dignam J, et al. Population differences in breast cancer: survey in indigenous African women reveals over-representation of triple-negative breast cancer. *J Clin Oncol*. 2009; 27(27):4515–21. [PubMed: 19704069]
17. Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, Waliszewska A, et al. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. *Proc Natl Acad Sci USA*. 2006; 103(38):14068–73. [PubMed: 16945910]
18. Sylvester BE, Huo D, Khramtsov A, Zhang J, Smalling RV, Olugbile S, et al. Molecular analysis of colorectal tumors within a diverse patient cohort at a single institution. *Clin Cancer Res*. 2012; 18(2):350–9. [PubMed: 22114137]
19. National Cancer Institute– Surveillance Research Program. [Accessed: Dec 27th, 2013] Cancer of the colon and rectum – SEER stat fact sheets. website Available at: <http://seer.cancer.gov/statfacts/html/colorect.html>
20. Meissner HI, Breen N, KLabunde CN, Vernon SW. Patterns of colorectal cancer screening uptake among men and women in the United States. *Cancer Epidemiol Biomarkers Prev*. 2006 Feb; 15(2): 389–94. [PubMed: 16492934]
21. Tepes B, Stabuc B, Stefanovic M, Bracko M, Frkovic Grazio S, Nowak Mlakar D, Maucec Zakotnik J. Faecal immunochemical test-based colorectal cancer screening programme SVIT in Slovenia: pilot phase. *Eur J Cancer Prev*. 2013 Epub 2013 Sep 10.

Figure 1. Overall survival of North American and West African patient

Figure 2.
Overall survival of North American and West African patients by stage of disease

Table 1
Patient and disease characteristics

	West Africa (n=160)	North America (n=1947)	<i>p</i>
Demographics			
Median age at diagnosis (IQR)	52 (36-65)	59 (49-69)	<0.01
Percent male	61.3	52.4	<0.01
Percent white	--	84.1	
Percent African-American	--	7.3	
Disease characteristics			
Percent presenting with obstruction	45.0	28.8	<0.01
Site, percentages			<0.01
Rectum	53.1	32.3	
Left Colon	20.6	35.6	
Right Colon	18.8	28.8	
Transverse Colon	5.6	5.2	
Other	1.9	3.1	
T-stage, percentages			<0.01
T0-2	0.6	29.5	
T3	7.5	52.3	
T4	91.9	18.2	
Presenting Stage, percentages			<0.01
I	0.6	0.0	
II	0.0	2.5	
III	41.3	49.5	
IV	58.1	48.0	

Bolded values are significant at $p < 0.05$

Table 2

Treatment

	West Africa (n=160)	North America (n=1947)	<i>p</i>
Neoadjuvant Chemotherapy, percentage	23.1	22.4	0.77
Adjuvant Chemotherapy, percentage *	44.4	49.6	0.26
Surgical Resection, percentages	(n=142)	(n=1657)	
Diverting Colostomy	23.6	0.1	
Abdomino-perineal resection	18.8	5.1	
Lower Anterior Resection	15.3	36.6	
Subtotal Colectomy	0.0	28.9	
Extended Right Hemi-Colectomy	20.1	25.2	
Left Hemi-Colectomy	6.9	8.6	
Sigmoid Colectomy	3.5	12.8	
Transverse Colectomy	5.6	1.5	
Other [†]	6.3	7.2	

* data unavailable for 18 West African patients and 290 North American patients (n=142 and 1657)

[†] Other includes biopsy only, appendectomy, diagnostic laparoscopy, exploratory laparotomy, proctectomy, colectomy and total pelvic exenteration

Table 3
Location of metastases amongst stage IV patients

	West Africa (n=93)	North America (n=932)	<i>p</i>
	%	%	<0.01
Liver only	2.2	48.1	
Peritoneal only	61.3	5.4	
Liver and peritoneum only	10.7	4.6	
Other combination	25.8	41.8	