Research Article

Cancer Epidemiology, Biomarkers & Prevention

Clinicopathologic Features of Colorectal Carcinoma in HIV-Positive Patients

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Abstract

Background: Emerging evidence suggests differences in colorectal cancer in HIV-infected patients (HIV^+) compared with HIV^- patients. Microsatellite instability (MSI), occurring in a subset of colorectal cancer, is present at a higher rate in certain cancers in HIV^+ patients. Colorectal cancer with MSI share some characteristics with those reported for HIV^+ colorectal cancer. On this premise, we studied clinical and pathologic features of HIV^+ colorectal cancer and evaluated for MSI using matched HIV^- colorectal cancer controls.

Methods: Two nested, matched cohorts were identified from a hospital-based cohort of colorectal cancer patients. HIV^+ colorectal cancers were identified and random control patients were matched for selected characteristics. Mismatch repair protein (MMR) IHC was performed as the detection method for MSI. Variables were compared between cases and controls using fixed-effects logit modeling to account for matching.

Results: We included 184 colorectal cancer samples (38 HIV^+, 146 HIV^- control). Median patient age at colorectal cancer onset was 55. When compared with HIV^- colorectal cancer, HIV^+ patients were more likely to have smoked ($P = 0.001$), have right-sided colorectal cancer (37% vs. 14%; $P = 0.003$), and tumor-infiltrating lymphocytes (TIL) above 50/10 high-power fields (21% vs. 7%). There was no difference in MMR protein expression ($P = 0.6$). HIV^+ colorectal cancer patients had reduced overall survival ($P = 0.02$) but no difference in progression-free survival.

Conclusions: HIV^+ patients developed colorectal cancer at a lower median age than population estimates, had a higher frequency of right-sided disease, and increased TILs, suggesting potential biologic differences compared with uninfected patients.

Impact: Clinicopathologic differences in colorectal cancer of HIV^+ persons may have implications for tumor pathogenesis. *Cancer Epidemiol Biomarkers Prev; 25(7); 1098–104. ©2016 AACR.*

Introduction

Non–AIDS-defining cancers (NADC) have become a major cause of mortality in the era of combined antiretroviral therapy due to the aging of the HIV/AIDS population (1). HIV-infected (HIV^+) persons are at increased risk for NADC compared with uninfected persons (2), a trend that is largely due to an excess risk of several tumors that include anal cancer, hepatocellular carcinoma, Hodgkin lymphoma, and lung cancer (2). Risk factors for certain cancers are well established such as such a higher prevalence of oncogenic viral coinfections (HPV, hepatitis B and C). Increased behavioral cancer risk factors have also been documented such as tobacco use and alcohol consumption (3, 4). Other poorly understood factors include chronic immunosuppression and inappropriate immune activation which are also suspected to play a role in tumorigenesis (5).

Colorectal cancer is the fourth leading cancer diagnosis in North America. Known risk factors for the development of colorectal cancer include polyposis syndromes, Lynch syndrome, and inflammatory bowel disease. A subset of colorectal cancer develops along the microsatellite instability (MSI) pathway sporadically or due to germline mutations in mismatch repair (MMR) genes. The hereditary prototype for germline mutations in MMR genes is Lynch syndrome which accounts for 3% to 4% of colorectal cancer. Lynch syndrome is defined by germline mutation in 1 of the 4 DNA MMR proteins *MLH1*, *MSH2*, *MSH6*, and *PMS2* resulting in a high level of MSI (MSI-H; refs. 6, 7). Alternatively, sporadic MSI-H develops as a result of promoter methylation of the *MLH1* gene and accounts for approximately 10% to 15% of colorectal cancer. Histopathologic features of MSI-H–related tumors include right-sided location, prevalent mucinous or medullary features, increased tumor-infiltrating lymphocytes (TIL), and a Crohn-like peritumoral lymphoid reaction (6). Immunohistochemical staining for DNA MMR proteins is an established and efficient method of identifying MSI-H (7).

HIV infection has not been found to confer increased risk for colorectal cancer in comparison with the general population or uninfected control populations (8). Nonetheless, emerging evidence suggests an atypical clinical experience in HIV^+ patients with colorectal cancer: earlier onset, higher tumor grade and stage, rapid disease progression, and lower performance status during treatment (9–14). These observations could reflect differences in screening, altered tumor immunity, and environmental or genetic factors that influence cancer development. MSI has been shown to be present at a higher rate in Kaposi sarcoma, lymphomas, and lung cancer in HIV^+ patients when compared with patients without HIV infection (15, 16). It is not known whether a higher rate of MSI occurs in colorectal cancers arising

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doi: 10.1158/1055-9965.EPI-15-1179

in HIV^+ patients. Understanding the role of MSI in colorectal cancers in these patients may be of biologic and clinical significance. Interestingly, MSI-H colorectal cancers share certain clinicopathologic characteristics with those reported thus far for colorectal cancers in HIV^+ patients such as early-onset and high tumor histologic grade.

On the above premises, we designed this study specifically aimed at (i) evaluating the clinicopathologic characteristics of colorectal cancers in HIV^+ patients using matched HIV negative (HIV^-) colorectal cancers as controls; and (ii) evaluating the frequency and associated clinicopathologic implications of MMR deficiency in colorectal cancers in HIV^+ patients.

Materials and Methods

Cohort selection

Two nested matched cohort studies were conducted within a single hospital-based cohort of 14,116 patients treated at our institution for a diagnosis of colorectal adenocarcinoma limited to ICD-O site codes of the large bowel (C182-189, C199, C209) between January 1, 1993 and June 1, 2014. Eligible cancer diagnoses included adenocarcinoma primary at any site in the large bowel, including the rectum and excluding the anus. Cases were identified using a database query in the same time period selecting for patients with the ICD-9 code for HIV infection (042). Validation of HIV infection was by clinical chart review and of cancer diagnosis by pathologist slide review. Clinical data was collected from routine patient assessments in the electronic medical record. The study was approved by the institutional review board.

A schematic of study design is presented in Fig. 1. For our first aim, we assessed for differences in clinical and pathologic variables including anatomic subsite of cancer (right/left), tumor histology, and survival. For each case, 2 to 3 control patients were selected by consecutive medical record number as a surrogate for calendar time and matching for year of birth (±5 years), year of colorectal cancer diagnosis (±2 years), sex, and race/ethnicity.

For the second aim, we evaluated for a difference in MMR protein expression by IHC. For the subset of cases identified in aim 1 with available tissue for IHC or prior results for MMR protein IHC on record, 2 to 3 control patients were selected by consecutive medical record number as a surrogate for calendar time and matching for year of birth (±5 years), sex, race/ethnicity, and anatomic subsite within the large bowel (right/left). Controls were not selected if tissue was not available for IHC unless prior results for MMR protein IHC were on record.

For both analyses, controls were not selected if they had HIV infection, if review of tumor histology had never been performed by pathologist at our institution, or if they received no treatment at our institution. Patients with <200 viral copies/mL and/or CD4 count >200 were considered to have well-controlled HIV infection at the time of cancer diagnosis. Progression-free interval was calculated from to the date of complete surgical resection to the date of radiographic detection of disease recurrence. For survival analysis, individuals with no date of death were censored at the last clinical appointment date and cause of death was determined from the last clinical assessment. In patients with metachronous colorectal cancer, clinical, and pathologic data was obtained from the first onset of colorectal cancer. For patients with synchronous colorectal cancer, pathologic data was obtained from the highest stage tumor.

Immunohistochemical analysis for MMR proteins

Immunohistochemical analysis for MMR proteins was used for the detection of MMR deficiency, and was performed on formalin-fixed paraffin-embedded tissue using 4-μm whole tissue sections. mAbs were used against MutS homolog 2, MSH2 (clone G219-1129, prediluted; Ventana), MutL Homolog 1, MLH1 (clone M1, prediluted; Ventana), MutS homolog 6, MSH6 (clone 44, prediluted; Ventana), and Postmeiotic Segregation Increased 2, PMS2 (clone EPR3947, prediluted; Ventana), following standard protocols recommended by the manufacturers. Control tissues included benign colorectal tissue and colorectal tumors with known Lynch syndrome by genetic analysis and a corresponding loss of MMR protein expression. Positive internal controls included nuclear staining in stromal or inflammatory cells. All stains were reviewed by a pathologist (C. Sigel). Tumors with positive nuclear reactivity were considered "normal," whereas complete absence of nuclear reactivity was considered "abnormal." Testing for MMR protein expression was not repeated for patients with results on record. Molecular analysis was not performed to correlate

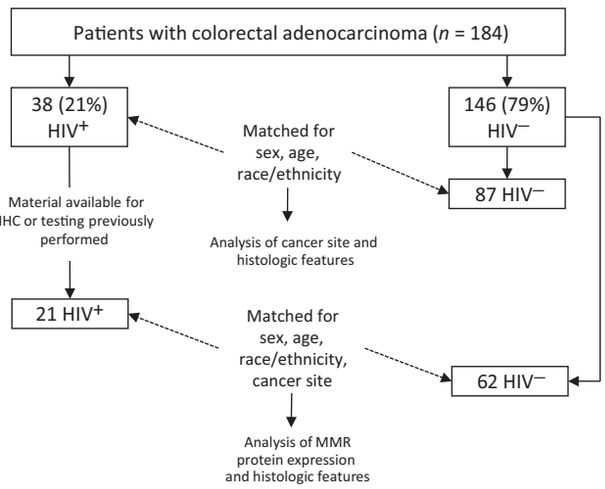

Figure 1.
Study design. MMR, mismatch repair. Percentages reflect proportion of preceding category.

MMR abnormalities with genetic status but prior molecular testing results were noted if on record.

Histologic assessment

Routinely prepared histologic sections obtained at the time of surgery from resected tumors were re-reviewed by one pathologist (M.S. Cavalcanti) unaware of HIV or MMR status. Tumors were evaluated for the presence or absence of a dysplastic precursor lesion adjacent to the infiltrating tumor. Tumor grade was assessed by the percentage of gland formation as low (>50%) or high (<50%). The mucinous component was assessed on the basis of the percentage of extracellular mucin as mucinous (>50%), with mucinous features (<50%), or nonmucinous (no mucin). TILs were identified by routine hematoxylin and eosin stain and were defined as lymphocytes admixed with carcinomatous epithelium. TILs were counted using an Olympus BX41 microscope with the total TIL count for 10 consecutive high-power fields recorded (high-power field = 0.238 mm^2). A peritumoral lymphoid reaction was defined as peritumoral lymphocyte predominant inflammation with reactive lymphoid follicles.

Statistical analysis

Mean age was compared between cases and controls using the *t* test. The distributions of demographic, clinical, and tumor characteristics were compared between cases and controls and differences were evaluated using fixed-effects logit regression to account for matching. We compared overall survival (OS), colorectal cancer–specific survival, and progression-free survival (PFS) using Kaplan–Meier methods, evaluating for statistical differences between strata using the log-rank test. All analyses were conducted using STATA Version 13 (Stata Corporation).

Results

HIV infection history

Thirty-eight case patients with colorectal cancer and HIV^+ were included. At cancer presentation, the median case age was 55 years (range, 32–73 years). The median length of known HIV infection prior to the diagnosis of cancer was 15 years (Table 1), ranging from zero (diagnosis during colon cancer treatment) to 27 years; the majority reported infection prior to 1996 [the beginning of the antiretroviral therapy (ART) era]. At cancer presentation, 31 patients were on ART (84%) with 25 (66%) having well-controlled disease at the time of cancer onset. Clinical history indicating previous poor HIV control (CD4 count nadir <200, history of AIDS-defining cancer, or opportunistic infection) was present in 24 individuals (63%). The opportunistic infections included pneumocystis pneumonia, candidal thrush, cytomegalovirus retinitis, pneumocystis jiroveci pneumonia, tuberculous pneumonia, central nervous system toxoplasmosis, chronic herpes simplex virus infection, herpes simplex virus encephalitis, cryptococcal infection, and cryptosporidiosis infection.

ADC was reported prior to colorectal cancer in 4 individuals: Burkitt lymphoma ($n = 1$), cervical invasive squamous cell carcinoma ($n = 1$), Kaposi sarcoma ($n = 1$), central nervous system lymphoma ($n = 1$). One or more NADC other than colorectal cancer occurred in 8 individuals as follows (NADC listed for each individual; summary in Table 1): non–small cell lung carcinoma and low-grade lymphoma (same patient); non–small cell lung carcinoma; multiple skin cancers (basal cell carcinoma/squamous cell carcinoma); laryngeal squamous cell carcinoma and multiple skin cancers (basal cell carcinoma/squamous cell carcinoma; same patient); gastric lymphoma; hepatocellular carcinoma and cholangiocarcinoma (same patient); renal cell carcinoma; and dermatofibrosarcoma protuberans. Three HIV^+ case patients had synchronous ($n = 2$) or metachronous ($n = 1$) colorectal adenocarcinomas. The majority of patients (82%, 31/38) were seen at the institution specifically for treatment of colorectal cancer, whereas 7 patients had sought care at this institution for a prior tumor or other condition. A minority of patients reported a history of hepatitis B, C, or HPV. Inflammatory bowel disease (ulcerative colitis) was reported in 2 patients.

Table 1. HIV infection history for patients with colorectal carcinoma

Characteristics, *n*, %	HIV^+ ($n = 38$)
HIV risk factor	
Unprotected sex—men who have sex with men	7 (18)
Unprotected sex—not otherwise specified	9 (24)
Intravenous drug use	5 (13)
Transfusion	1 (3)
Needle stick	1 (3)
Unknown	15 (40)
HIV infection average duration prior to cancer presentation, years (range)	14.7 (0–27)
HIV diagnosis prior to 1996	28 (74)
Colorectal cancer diagnosis after 2000	35 (92)
Prior history of poor HIV control	
CD4 count nadir <200	7 (18)
Opportunistic infection	21 (55)
AIDS-defining cancer	4 (11)
One or more of above	24 (63)
Other non–AIDS-defining cancer[a]	8 (21)
Prior to colorectal carcinoma	3
After colorectal carcinoma	4
Concurrent	1
Average $CD4^+$ cells/mm^3 at cancer presentation, years (range)	404 (range 20–1,489)
HIV viral load copies/mL undetectable[b] at cancer presentation	17 (45)
Well-controlled HIV at cancer diagnosis[c]	25 (66)

[a]Excludes metachronous or synchronous colorectal carcinoma.
[b]Undetectable generally <50 copies/mL.
[c]<200 copies/mL or CD4 count >200 cells/mm^3.

Clinical and pathologic features of HIV-associated colorectal cancer

A total of 184 individuals with colorectal cancer were included comprising 38 HIV^+ and 146 HIV^- controls. Clinical and pathologic findings are summarized in Table 2. Demographic variables for the cases and controls did not differ after matching. HIV^+ patients smoked at a higher frequency compared with controls ($P = 0.001$). There was a higher frequency of TILs in HIV^+ patients (>50 TILs/10 HPF: 21% vs. 7%) and a lower frequency of absent TILs (14% vs. 36%; $P = 0.02$). The distribution of cancer stage at presentation was similar between the groups. HIV^+ patients had reduced OS ($P = 0.02$; Fig. 2) but no difference in PFS or colorectal cancer–specific survival (both $P > 0.1$).

Nested analysis of 38 HIV^+ patients and 87 HIV^- matched controls showed a higher frequency of right-sided carcinoma (37% vs. 14%; $P = 0.003$; Table 3). There was no significant difference in clinical cancer presentation by screening or by

Table 2. Patient demographic data and histologic variables[a]

Characteristics, *n*, %	HIV$^+$ (*n* = 38)	HIV$^-$ (*n* = 146)	*P*
Male	27 (71)	108 (74)	0.7
Age, median, IQR	55 (51–66)	55 (49–65)	0.9
Race/ethnicity			
White	13 (34)	72 (49)	0.005
Black	14 (37)	39 (27)	
Hispanic	9 (24)	10 (7)	
Other	2 (5)	25 (17)	
Smoking status			0.001
Current smoker	12 (32)	16 (11)	
Former smoker	16 (42)	53 (36)	
Never smoker	10 (26)	77 (53)	
Cancer stage at presentation			0.4
In situ	5 (14)	6 (4)	
I	3 (8)	15 (11)	
II	7 (19)	27 (19)	
III	12 (33)	50 (36)	
IV	9 (25)	41 (30)	
TILs			
0	4 (14)	36 (36)	0.02
1–50	19 (66)	56 (57)	
50–100	5 (17)	5 (5)	
>100	1 (4)	2 (2)	
Peritumoral lymphoid aggregates	3 (17)	6 (8)	0.3
Mucinous histology			0.2
Mucinous (>50%)	6 (16)	9 (6)	
Features (<50%)	7 (18)	26 (18)	
No mucin	25 (66)	106 (75)	

Abbreviation: IQR, interquartile range.

[a]Staging and histologic data were not available for some patients with limited biopsy material.

symptoms. No differences in tumor grade, presence of precursor lesion, mucinous histology, or peritumoral lymphocytes were observed.

MMR protein IHC

The second nested analysis included 21 HIV$^+$ patients and 62 HIV$^-$ controls. Demographic variables and tumor subsite for the cases and controls did not differ and supported appropriate matching. Loss of MMR protein expression was detected at a similar rate in the two groups: 14% ($n = 3$) and 11% ($n = 7$; $P = 0.6$), respectively (Table 4). The 3 case patients with MMR abnormalities comprised the following staining patterns and molecular abnormality (if on record): MLH1/PMS2 loss with corresponding *MLH1* germline mutation, PMS2 loss with MSI high (no germline testing performed), and MLH1/PMS2 loss with no known genetic testing.

TILs and histology were reanalyzed to see whether histologic differences were maintained in this component of the study because it represented a subset of the entire group. All previous findings persisted in this subset of cases: a higher frequency of TILs (>50 TILs/10 HPF: 29% vs. 6%) and a lower frequency of absent TILs (12% vs. 69%; $P = <0.001$). Similarly, no differences in grade, mucinous histology, or peritumoral lymphocytes were seen.

Discussion

This series of 38 patients is the largest report, to our knowledge, of the clinical and histopathologic features of colorectal cancer in HIV$^+$ persons and is the first report to systematically evaluate for MMR expression.

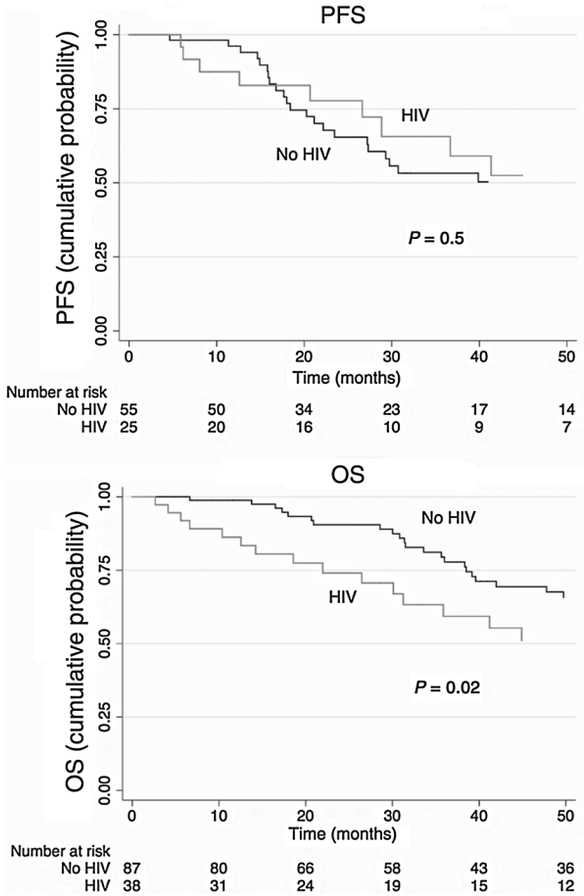

Figure 2.
PFS (top) and OS (bottom) for colorectal carcinoma in HIV$^+$ patients and HIV$^-$ controls with corresponding *P* value.

Prior reports of colorectal cancer in HIV$^+$ persons include case series, case–control studies, and a single retrospective multi-institutional study (10, 12, 13, 17). Similar to prior reports, case patients in the current study had an early onset of cancer (median 55 years) compared with population-based (Surveillance Epidemiology and End Results) estimates (median 69 years). Our cohort was comprised of men and women of diverse racial and ethnic backgrounds with diverse HIV risk factors, a longer history of HIV infection before cancer onset, and with the majority having well-controlled HIV infection at the time of cancer diagnosis. We found that HIV$^+$ patients were more likely to have smoked compared with HIV$^-$ colorectal cancer patients. Smoking is a known behavioral risk factor for cancer, including colorectal cancer (18), found with a higher prevalence in HIV$^+$ individuals (19–21).

Although there was no difference in tumor grade or stage by HIV status in our analyses, we did find clinicopathologic differences occurring in colorectal cancer in HIV$^+$ persons with implications for tumor pathogenesis. First, they were more likely to occur in the right colon. This finding differs from the usual anatomic distribution of colorectal cancer which occurs more frequently in the sigmoid and rectum, and is corroborated by the distribution of the control group (22). Also, our study is

Table 3. Analysis of clinicopathologic variables for colorectal adenocarcinoma in HIV$^+$ persons and matched HIV$^-$ controls

Characteristics, *n* (%)	HIV$^+$ (*n* = 38)	HIV$^-$ (*n* = 87)	*P*
Clinical presentation			0.07
Asymptomatic	2 (5)	0 (0)	
Screening	8 (21)	26 (31)	
Symptomatic	28 (74)	58 (69)	
Other cancer[a]	10 (26)	12 (14)	0.09
Colorectal cancer anatomic site			0.003[b]
Left	24 (63)	75 (86)	
Rectum	15 (63)	37 (49)	0.008[c]
Right	14 (37)	12 (14)	
Precursor lesion(s)			0.1
Not identified	7 (35)	12 (36)	
Tubular adenoma	14 (42)	4 (20)	
Tubulovillous adenoma	7 (21)	9 (45)	
Sessile serrated adenoma	0	0	
Grade			0.6
High grade	6 (18)	11 (13)	
Low grade	28 (82)	71 (87)	
Insurance			0.07
Private	25 (66)	3 (3)	
Medicare	11 (29)	11 (13)	
Medicaid	2 (5)	73 (84)	

[a]Includes AIDS-defining and non–AIDS-defining cancers (two individuals had a history of both); excludes multiple colorectal carcinoma.
[b]*P* value reflects right versus left.
[c]*P* value reflects right, left (nonrectal), and rectum.

the first to report that colorectal cancer in HIV$^+$ persons have increased TILs. Given that tumors with high levels of MSI are frequently located in the cecum and exhibit increased CD8$^+$ TILs (23), an association between HIV$^-$ colorectal cancer and MSI was hypothesized, but we detected no difference in frequency of MMR abnormalities suggesting that MSI is not the underlying cause.

There are currently no HIV-specific recommendations regarding colorectal cancer screening (24). We detected no difference in cancer presentation (symptomatic vs. detection by screening) between the groups.

HIV infection was associated with worse OS (but not PFS or colorectal cancer –specific survival) in our study. Poorer OS in HIV$^+$ patients was likely due to HIV-related morbidity/non-colorectal cancer–specific morbidity. Cancer treatment disparities have also been seen in HIV-infected patients compared with uninfected patients, which could also contribute to worse OS (13, 25). We did not address differences in performance status and cancer therapy between the two populations, but note that no patients died of HIV-related complications during cancer treatment. Furthermore, we cannot account for any contribution of prior cytotoxic therapy for other cancers that may have had an effect on the development of colorectal cancer, development of other cancers in this population, and OS.

Our study found an increased rate of smoking in HIV patients with colorectal cancer, but we cannot draw any conclusions for a causal association or provide insight into the impact of smoking on clinical and pathologic features of HIV$^+$ colorectal cancer. Of note, smoking-related colorectal cancer risks have been reported to be higher for proximal than distal colorectal cancer (26). Samowitz and colleagues reported associations between smoking and colon cancer may be explained by an association with the CpG island methylator phenotype and BRAF mutations irrespective of MSI status (27). These factors are worthy of further investigation in this population. The tumorigenic effects of other long-term exposures, lifestyle factors, and conditions occurring in HIV infection and therapy are also unclear. Alterations to the gut in well-controlled HIV include persistent mucosal inflammation, immune activation, impaired mucosal immunity, and disrupted gut microbiota (28). These factors could also impact development, progression, and morbidity of colorectal cancer.

A study strength was the inclusion of control patients treated in the same institution matched for time of cancer diagnosis. In addition, our case patients exhibited both genders, a majority of patients with well-controlled HIV at cancer onset, and varied risk factors for HIV infection, whereas prior studies have been limited by being composed by low case numbers, exclusively male patients (9, 10) and patients with AIDS only or poorly controlled HIV at cancer onset.

Limitations to the current study, particularly survival analysis, include a relatively small sample size and retrospective design. The majority of patients were referred to the institution for cancer care and HIV infection history was primarily by clinical report. The status of HIV disease management was typically evaluated at the time of cancer presentation, but for the majority of patients, documentation of long-term HIV control was not available such as CD4 nadir, ART duration,

Table 4. Colorectal carcinomas in HIV$^+$ persons and matched HIV$^-$ controls with MMR protein immunohistochemical stain results and histologic variables

Characteristics, *n* (%)	HIV$^+$ (*n* = 21)	HIV$^-$ (*n* = 62)	*P*
Cancer site			
Left	13 (62)	40 (65)	1.00
Right	8 (38)	22 (35)	
Grade			0.6
High grade	4 (22)	10 (16)	
Low grade	14 (78)	51 (84)	
TILs			<0.001
0	2 (12)	34 (69)	
1–50	10 (59)	12 (25)	
50–100	5 (29)	2 (4)	
>100	0 (0)	1 (2)	
Peritumoral lymphoid aggregates	2 (15)	3 (9)	0.6
Mucinous			0.5
Mucinous (>50%)	4 (19)	6 (10)	
Features (<50%)	5 (24)	11 (19)	
No mucin	12 (57)	41 (71)	
MMR protein IHC			0.6[a]
Abnormal	3 (14)	7 (11)	
Not abnormal	18 (86)	55 (89)	
MLH1			0.7[a]
No staining	2 (10)	4 (6)	
Positive staining	58 (94)	19 (91)	
PMS2			0.3[a]
No staining	3 (14)	4 (7)	
Positive staining	18 (86)	58 (94)	
MSH2			**[b]
No staining	0 (0)	4 (7)	
Positive staining	21 (100)	58 (94)	
MSH6			**[b]
No staining	0 (0)	4 (7)	
Positive staining	21 (100)	21 (93)	

[a]Significance testing with fixed-effects logit model to account for matching/clustering.
[b]Test could not converge.

and compliance. Incomplete data for these parameters may have limited implications as prior investigations by Bini and colleagues have found no association between colorectal cancer and duration of HIV infection, viral load, or CD4 count (9). We cannot entirely exclude whether referral bias impacted results as the study was conducted in a specialized cancer hospital. Although it did not reach clinical significance, differences in insurance provider may reflect differences in the populations also impacting survival.

In our series of nested matched cohort studies, we have demonstrated that colorectal cancer in HIV^+ persons may have an earlier age of onset and a higher frequency of right-sided disease which may inform screening practices. We have also observed higher rates of tumor lymphocyte infiltration in colorectal cancer in HIV^+ persons without an increase in MMR protein abnormalities potentially suggesting altered colorectal cancer tumor biology or host–immune interaction not attributable to MSI.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: C. Sigel, J. Shia, K. Sigel
Development of methodology: C. Sigel, J. Shia, K. Sigel
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Sigel, M.S. Cavalcanti
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C. Sigel, E. Vakiani, K. Sigel
Writing, review, and/or revision of the manuscript: C. Sigel, M.S. Cavalcanti, T. Daniel, E. Vakiani, J. Shia, K. Sigel
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C. Sigel, T. Daniel

Acknowledgments

The authors thank Dr. Luis Chiriboga for excellent laboratory support.

Grant Support

This research was funded in part through the NIH/NCI (P30 CA008748 to C. Sigel and K07 CA180782 to K. Sigel). Histology services were provided in part by the Memorial Sloan Kettering Cancer Center Pathology core laboratory and the NYU Medical Center IHC core laboratory. The IHC core laboratory at NYU Medical Center is partially funded by The Laura and Isaac Perlmutter NCI Cancer Center Support Grant (NIH/NCI P30CA016087), and NIH/ORIP S10 Shared Instrumentation Grants (NIH/ORIP S10OD01058 and NIH/ORIP S10OD018338).

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Received November 17, 2015; revised April 7, 2016; accepted April 7, 2016; published OnlineFirst May 13, 2016.

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