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WORD COUNT 4134
TIME SUBMITTED 07-DEC-2023 02:01PM
PAPER ID 105166022

Name of Journal: *World Journal of Gastrointestinal Surgery*

Manuscript NO: 87155

Manuscript Type: ORIGINAL ARTICLE

Retrospective Cohort Study

Oncological features and prognosis of human immunodeficiency virus-positive colorectal cancer using propensity score matching: a retrospective study

Oncological features of HIV-positive colorectal cancer

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Abstract

BACKGROUND

Given the prolonged life expectancy and increased risk of colorectal cancer (CRC) among people with human immunodeficiency virus (HIV), the prognosis and pathological features of CRC in patients with HIV should be examined.

AIM

This study aimed to compare the differences in oncological features, surgical safety, and prognosis between patients with and without HIV who had CRC at the same tumor stage and tumor site.

METHODS

In this retrospective study, we collected data from 24 patients with HIV and CRC who underwent radical resection for CRC. Using random stratified sampling, 363 postoperative patients with colorectal adenocarcinoma without HIV infection were selected. Using propensity score matching, we selected 72 patients (HIV positive: HIV negative=24:48). Differences in basic characteristics, HIV acquisition, perioperative

serological indicators, surgical safety, oncological features, and long-term prognosis were compared.

RESULTS

Fewer patients with HIV underwent chemotherapy compared to patients without HIV. Additionally, they had fewer preoperative and postoperative leukocytes, fewer preoperative lymphocytes, lower carcinoembryonic antigen levels, more intraoperative bleeding, more metastatic lymph nodes, higher node stage, higher tumor node metastasis stage, shorter overall survival, and shorter progression-free survival compared with patients who were HIV negative.

CONCLUSION

Compared with patients with CRC who were HIV negative, patients with HIV and the same tumor stage and tumor site had more metastatic lymph nodes and worse long-term survival after surgery. Standard treatment options for patients with HIV and CRC should be explored.

Key Words: Colorectal cancer; HIV; Propensity score matching; Oncological features; Surgical safety; Prognosis

Yang F, He F, Chen D, Tang C, Woraikat S, Li Y, Qian K. Oncological features and prognosis of HIV-positive colorectal cancer using propensity score matching: a retrospective study. *World J Gastrointest Surg* 2023; In press

Core Tip: This study aimed to compare the differences in oncological features, surgical safety, and prognosis between patients with and without HIV with colorectal cancer at the same tumor stage and tumor site. Patients with HIV and colorectal cancer have more metastatic lymph nodes and worse long-term survival compared to patients without HIV at the same tumor stage; however, the risk of surgery is not increased. Our

series of 24 postoperative patients represents the largest reported study of patients with HIV who have colorectal cancer.

INTRODUCTION

Since the general acceptance of highly active antiretroviral therapy (HAART) in 1996, the survival period for patients with Acquired Immune Deficiency Syndrome (AIDS) has significantly increased, and the incidence rates of AIDS-defined cancers, Kaposi's sarcoma, non-Hodgkin lymphoma, and cervical cancer have significantly decreased [1-5]. However, the incidence rates of non-AIDS-defining cancers, such as colorectal cancer (CRC), liver cancer, lung cancer, anal cancer, and Hodgkin's disease, have increased [6, 7], which is related to the prolonged life expectancy of patients with AIDS. These non-AIDS-defining cancers account for an increasing number of deaths among carriers of human immunodeficiency virus (HIV). According to GLOBOCAN 2020 [8] data, approximately 1.93 million new cases of CRC worldwide were recorded in 2020, ranking third in malignant tumors (10.0%), only after breast cancer (11.7%) and lung cancer (11.4%). In addition, approximately 930,000 (9.4%) people died after only lung cancer (18.0%), ranking second in malignant tumors. The global number of new cases and deaths from CRC is increasing yearly. Compared to the general population, patients with AIDS have an increased incidence rate of CRC, an earlier age of invasion, and more advanced stages of disease [9].

During the CRC resection, our team discovered more suspicious positive lymph nodes in patients with CRC and HIV. However, considering the same tumor stage and tumor site, differences in oncological features and prognoses between patients with CRC with and without HIV have rarely been reported. With the prolonged life expectancy and increased risk of CRC among people with HIV, it is important to understand the prognosis and pathological features of CRC in patients with HIV. Therefore, in this study, we aimed to compare the differences in oncological features, surgical safety, and prognoses between patients with and without HIV who had CRC at the same tumor stage and tumor site.

MATERIALS AND METHODS

Patients and methods

We extracted the clinical data of patients who were diagnosed with CRC complicated with HIV infection and underwent radical CRC resection between January 1, 2012, and March 31, 2022. Twenty-four cases were retrieved. After analysis, we observed that the pathological classification of all patients with HIV and CRC was adenocarcinoma, and no preoperative neoadjuvant chemotherapy or radiotherapy was administered. However, because our hospital conducts more than 1,000 radical CRC operations every year, to control the sample size, we used random stratified sampling to collect the data of 363 patients who had not received preoperative neoadjuvant chemotherapy and radiotherapy, were HIV negative with colorectal adenocarcinoma, and had undergone radical CRC resection. We collected data on demographic characteristics, basic preoperative profile, preoperative HIV treatment, perioperative serological indicators, surgical outcomes, oncological characteristics, and patient survival. The authors did not utilize any artificial intelligence tools.

Statistical analysis

Propensity score matching (PSM) analysis is widely used because it minimizes intervention or patient selection bias in non-randomized controlled studies and observational studies [10]. We used PSM to pair patients who were HIV positive and HIV negative to reduce the impact of differences in baseline data between patients with and without HIV on the results, especially the effect on the number of metastatic lymph nodes. Before matching, we identified a cohort of patients with nearly 15 times as many patients without HIV as patients with HIV. However, matching at 1:1 would have resulted in substantial data loss and reduced the statistical power. Therefore, we matched at 1:2. Baseline data and variables that may affect the number of peri-intestinal lymph node metastases were used to construct propensity scores, including age, sex, tumor site, degree of tumor differentiation, and tumor stage. The matching package was used to match the data for propensity scores, and 1:2 matching was adopted, with a

caliper width limit of 0.1*standard deviation of the logarithmic score. The matched groups were considered balanced if the standardized mean difference between them after matching was less than 0.1 [11]. Categorical variables were expressed as frequencies (%), and continuous variables were expressed as medians (P25, P75). Categorical variables were analyzed using Fisher's exact or Chi-square tests, and continuous variables were analyzed using the Mann–Whitney U test. Statistical significance was set at $p<0.05$. The Kaplan–Meier method was used to compare the overall survival and progression-free survival periods between the two groups, and the log-rank test was used to determine whether the differences were significant. Calculation of propensity scores and selection of the matched cohort were performed using R version 4.0.2 (R Foundation for Statistical Computing, 2020) with the MatchIt package. Other statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A biomedical statistician performed a statistical review of the study.

RESULTS

Baseline Data

Twenty-four patients with HIV and 363 patients without HIV were included, and 72 were matched by propensity scores (HIV-positive: HIV-negative = 24:48, Table 1). Although the differences in all variables were not significant before and after matching, the differences in baseline data, such as tumor site, degree of differentiation, tumor stage, and age, decreased after matching.

Basic features

After PSM, fewer patients with than without HIV received chemotherapy [29.2% vs. 62.5%, P = 0.008], whereas the differences in CRC family history, main complications, smoking, drinking, abdominal surgery history, body mass index, and adverse reactions to chemotherapy were not significant (Table 2). All patients with HIV had latent disease, and no opportunistic infections were recorded. Fifteen patients were diagnosed with HIV before admission, others were found to have HIV infection during preoperative screening. Fourteen patients were undergoing HAART before admission.

Most patients were infected with HIV through sexual transmission. The median time difference between HIV and CRC diagnosis was 32 mo (range: 1–192 mo), the median CD4+ cell count before surgery was 459 cells/mm^3 (range: 158–1,090), and the CD4+/CD8+ median was 0.71 (range: 0.22–2.10). At the follow-up of the patients with AIDS, only 1 patient was not medication adherent.

Postoperative outcomes

Table 3 presents the major peripheral venous blood indicators of the 72 patients. Compared to patients without HIV, patients with HIV had lower postoperative leukocytes [5.36 (3.85, 6.70) vs. 5.92 (4.95, 7.50), P = 0.49], fewer postoperative leukocytes [6.91 (5.36, 8.84) vs. 8.98 (6.97, 10.89), P = 0.013], fewer preoperative lymphocytes [1.19 (0.77, 1.48) vs. 1.48 (1.18, 1.90), P = 0.028], and lower carcinoembryonic antigen (CEA) levels [2.27 (1.38, 3.10) vs. 5.44 (2.90, 20.00), P = 0.012]. No significant differences were observed in preoperative and postoperative hemoglobin, postoperative lymphocytes, preoperative albumin, postoperative albumin and carbohydrate antigen 19-9 levels, or American Society of Anesthesiologists score. Surgical safety between the HIV-positive and negative groups is shown in Table 4. Patients with HIV experienced more intraoperative blood loss than those without HIV [100 (50,100) vs. 50 (35,100), P = 0.46]; however, no significant difference was observed between the two groups in terms of operation time, time to first flatus, time to first defecation, time to first liquid intake, time to ambulation, postoperative hospital stay, postoperative complications, admission to intensive care unit, time to discontinuing antibiotics, hospitalization expenses, performance status 1 mo after operation, long-term postoperative gastrointestinal discomfort, decrease in hemoglobin and albumin levels, intraoperative blood transfusion, enterostomy, or American Society of Anesthesiologists score. Two patients in each group had distant metastasis before operation, 1 patient in the HIV-positive group had liver and lung metastasis, and 3 patients had only liver metastasis. No readmissions or deaths were recorded within 1 mo in either group. The median follow-up time for both HIV-positive and matched controls was 31 mo (2–91). Ten patients (41.7%) died (9 from cancer and 1 from other causes) in the HIV-positive group, and 7

(14.6%) died in the control group (6 from cancer and 1 from other causes). Patients with HIV and CRC had a reduced overall survival (26 mo and 37 mo, respectively) and progression-free survival (23.5 mo and 37 mo, respectively) compared with the matched controls. The differences in overall survival (P = 0.007) (Figure 1) and progression-free survival (P = 0.035) (Figure 2) between the two groups were significant. However, two missing patients were recorded in each group at the postoperative follow-up.

Oncological features

Patients with HIV had more lymph node metastases than patients without HIV [1 (0, 3.5) vs. 0 (0, 0), P = 0.001], higher node stage [1 (0, 1.75) vs. 0 (0,1), P = 0.005], and higher tumor node metastasis (TNM) stage [3 (2, 3) vs. 2 (2, 2.75), P = 0.004], whereas the harvested lymph nodes, size of the largest lymph node, metastasis, tumor size, MSI (Microsatellite instability), RAS (Rat sarcoma) gene mutation, BRAF (Serine/threonine protein kinase B-raf) gene mutation, MLH1 (MutL homologue 1), MSH (Melanocyte-stimulating hormone)2, MSH6, and Ki-67 (antigen identified by monoclonal antibody Ki-67) were not significantly different. No cases with positive margins were recorded in either group (Table 5). Table 6 shows the number of metastatic lymph nodes, node stage, and TNM stage at different tumor stages.

DISCUSSION

To our knowledge, no studies have reported differences in the postoperative pathological features between patients with a combination of HIV and CRC and patients with CRC alone at the same tumor stage and tumor site. In this study, after matching factors that may affect lymph node metastasis in CRC using PSM, by comparing the oncological characteristics, surgical safety, and prognosis of the two groups of patients, we discovered that patients with HIV had significantly more lymph node metastases than patients without HIV (Table 5). This may be related to immunosuppression in patients with HIV. In addition, patients with HIV had higher node and TNM stage than patients without HIV. Regarding surgical outcomes, although patients with HIV had more intraoperative blood loss than patients without

HIV, the difference in the decrease in hemoglobin levels between the two groups was not significant. The significant increase in intraoperative blood loss in patients with HIV may be etiologically related to AIDS-defining illnesses, other comorbidities, lifestyle, and etiologies related to underlying HIV infection [12, 13], and intraoperative blood loss was the expected value for the attending surgeon. Therefore, we concluded that the surgical safety of radical CRC surgery in patients with HIV was not worse than that of patients without HIV. However, the overall survival and progression-free survival were shorter in patients with HIV than in patients without HIV.

CEA levels of patients with HIV and CRC were lower than those of patients without HIV. Normal and cancerous tissues produce approximately the same amount of CEA [14, 15]. Healthy adults excrete approximately 50–70 mg of CEA daily in their feces [14]. Most of the CEA produced by the human body is excreted through the intestine. CEA may also function in innate immunity [16, 17] and prevent microorganisms from invading the intestinal epithelial cells [17]. However, owing to immune deficiency, the intestinal mucosa of people with HIV has decreased resistance to intestinal flora, resulting in more CEA being released into the intestine to resist microorganisms. Conversely, the blood CEA level decreases [16, 17].

The incidence rate of CRC in China has increased from 17.1/100,000 in 2013 to 26.4/100,000 in 2020 [8, 18]; thus, we estimated that the total incidence rate of CRC in China in the last 10 years was 220/100,000. In addition, 64,000 patients with AIDS survived, and 21,000 died in our region as of October 2022. Therefore, we estimated that approximately 140 patients with AIDS and CRC were diagnosed in our region over the past 10 years. Admittedly, this estimation method is inaccurate, as we did not consider the influence of AIDS on the incidence of CRC and the different incidences of CRC in different regions of China. However, since we did not have data on HIV-positive patients with CRC in our region, we used this rough method for estimation.

According to our hospital data, 65 cases of HIV-positive colorectal adenocarcinoma were recorded during the study period; considering that some patients were not treated, we believe that our hospital admitted more than half of the patients with HIV

and CRC in our province, which is a relatively high proportion. Although the sample size of the HIV-positive group was only 24, which was limited by the inclusion criteria and the low incidence of AIDS, we believe that the sample size of our study was not small. The study by Wasserberg *et al* included only 11 HIV-positive patients with CRC [19], and some of these patients did not undergo surgery. Another study [20] included 27 patients with HIV and CRC and compared the clinical presentation and prognosis of patients with and without HIV. Only 4 HIV-positive patients underwent surgery. To date, our series of 24 postoperative patients represents the largest study of patients with HIV and CRC reported in the literature.

Whether HIV increases the risk of CRC remains controversial. Most studies suggest that HIV decreases immunity and HARRT increases life expectancy in patients with HIV, leading to an increased risk of malignancy [6, 7, 21, 22]. Some studies have reported no difference in CRC prevalence between patients with and without HIV [23]. Conversely, some have suggested that patients with HIV have a lower risk of CRC [24]. Reinhold *et al* [21] discovered that patients with HIV were less likely to undergo CRC screening tests than uninfected patients. This may account for the lower risk of CRC reported by some studies in patients with HIV.

In addition, we observed that patients with HIV were less likely to undergo chemotherapy than patients without HIV, similar to the report of Suneja *et al* [25, 26]. Differences in access to cancer treatment may partially explain the shorter survival of patients with HIV and cancer. Suneja *et al* suggested that many treatment providers may believe that patients with HIV are in poorer organismal condition, less tolerant of treatment, and less likely to adhere to treatment than patients without HIV, thus reducing their chances of receiving systemic therapy. In addition, the lack of specific treatment guidelines for patients with HIV and cancer is an important reason for the low proportion of patients with HIV receiving systemic therapy [26]. From the patient's perspective, those with HIV may be more reluctant to receive systemic therapy for oncology because of concerns about chemotherapy side effects, an inadequate understanding of the need for cancer treatment, or the burden of the dual management

of cancer and HIV [25]. However, there may be additional reasons why patients with HIV and CRC have a worse long-term prognosis than those without HIV. Further high-quality studies are needed to explore these reasons.

Available data suggest that with HIV and CRC are more severely ill and younger than those without HIV infection [9]. Berretta *et al* [20] compared the clinical presentation and outcomes of 27 patients with HIV and 54 age- and sex-matched CRC controls and concluded that patients with HIV had poorer performance status and unfavorable Dukes stages. Bini *et al* [9] published the results of a screening colonoscopy study in which the prevalence of colon cancer was assessed in 136 asymptomatic patients with HIV who were ≥ 50 years old and 272 asymptomatic uninfected controls with CRC by matching age, sex, and CRC family history. The authors discovered that the prevalence of neoplastic lesions was significantly higher in patients with HIV than in controls, even after adjusting for potential confounding variables. In this study, although we eliminated the age difference after PSM, patients with HIV still had significantly more metastatic lymph nodes than patients without HIV (Table 5), and overall survival and progression-free survival were significantly shorter in patients with HIV than in those without HIV (Figures 1 and 2). This result is consistent with the findings of Berretta *et al* [20]

Berretta *et al* [27] and André T, *et al* [28] concluded that the combination of HAART did not increase the toxicity of FOLFOX4. Currently, the advantages of immunotherapy are being gradually explored. Patients with HIV have reduced immunity, regardless of the CD4 count; thus, because of the fear of increased HIV viral replication and increased toxicity in the presence of T-cell activation [29], they are usually excluded from trials of immune checkpoint inhibitors, and we currently lack data on the efficacy of immunotherapy in this population. The safety and efficacy of immunotherapy for HIV-infected malignancies remain unclear. The phase 1 trial by Uldrick TS *et al* revealed that PD-1 monoclonal antibodies are safe for use in patients with HIV who are on HAART and have CD4+ T-cell counts above 100 cells/μL [30]. In addition, the results of Cao *et al*

demonstrated that PD-L1/PD-1 interactions may induce an immune environment favorable for tumor development [31].

Chemotherapy and immunotherapy have a better safety profile during CRC treatment in patients with well-controlled HIV infection; however, caution should be exercised when treating patients with more severe disease and advanced immunosuppression. Notably, HAART with prophylaxis for opportunistic infections should be administered during treatment, and patients should be closely monitored for CD4+ cells and serum viral levels. Nonetheless, the reasons for poorer CRC prognoses in patients with HIV are unclear and may be due to more advanced diagnosis and inadequate treatment [32] or may be influenced by decreased immune function.

This was a retrospective study; however, we used PSM to reduce the differences in baseline data between the two patient groups and to minimize the impact of baseline differences on the outcomes. This allowed better comparison of the postoperative oncological characteristics, surgical safety, and prognosis of patients with and without HIV who had CRC at the same tumor stage and tumor site and who underwent radical CRC resection. Therefore, we believe that the methodology of our study is scientific and that the conclusions are reliable and meaningful. However, we could not obtain specific data on AIDS-related symptoms and preoperative or postoperative HAART treatment. As mentioned earlier, patients with HIV are more reluctant to receive postoperative adjuvant therapy for malignancies. In addition, standard treatment protocols may be unavailable for patients who live with poorly controlled HIV infection. Therefore, clinicians should direct their attention providing patients with prompt treatment, and scientists should work more quickly to develop appropriate treatments. Moreover, the treatment process should be monitored. We hope that more in-depth studies will be conducted to focus on the efficacy and safety of adjuvant therapy in malignant tumors, to further clarify the interactions of HIV with malignant tumors, and to develop more appropriate treatment plans.

This study had some limitations. Firstly, although our study had a larger sample size than most AIDS-related clinical studies, limited by the prevalence of AIDS, the

sample size of this study is small compared to that of other studies examining the relationship between common diseases and CRC. Secondly, we did not analyze the relationship between the severity of HIV infection and the prognosis of colorectal cancer in the HIV-positive group. Thirdly, because of the small sample size of the two groups of patients with different tumor stages (Table 6), their differences were not compared. Fourthly, we did not specifically analyze the differences in the regimen and cycles of chemotherapy treatments between the two groups of patients. Studies with larger sample sizes are expected to further reveal the impact of HIV infection on the oncologic characteristics, prognosis, and safety of surgery in CRC.

CONCLUSION

Compared to patients with CRC and without HIV, those with HIV with the same tumor stage and tumor site have a higher number of lymph node metastases and worse postoperative long-term survival; however, the risk of surgery is not increased. Overall, patients with HIV and CRC have a worse prognosis. Therefore, clinicians should focus on treating this population more aggressively and should explore standard treatment options for patients with HIV and CRC. We look forward to further studies on HIV-associated malignancies.

ARTICLE HIGHLIGHTS

Research background

Human immunodeficiency virus (HIV) infection may accelerate the progression of colorectal cancer. Given the prolonged life expectancy and increased risk of colorectal cancer (CRC) among people with HIV, the prognosis and pathological features of CRC in patients with HIV should be examined. This study aimed to compare the differences in oncological features, surgical safety, and prognosis between patients with and without HIV who had CRC.

Research motivation

The same tumor stage and tumor site, differences in oncological features and prognoses between patients with CRC with and without HIV have rarely been reported. Therefore, we aimed to compare the differences in oncological features, surgical safety, and prognoses between patients with and without HIV who had CRC at the same tumor stage and tumor site.

Research objectives

In this study, after propensity score matching (PSM), by comparing the oncological characteristics, surgical safety, and prognosis of the two groups of patients, we concluded that the surgical safety of radical colorectal cancer surgery in patients with HIV was not worse than that of patients without HIV. However, the overall survival and progression-free survival were shorter in patients with HIV than in patients without HIV. More attention should be given to them, clinicians should encourage them to actively treat and scientists should work more quickly to develop appropriate treatments.

Research methods

In this study, after matching factors that may affect lymph node metastasis in CRC using PSM, by comparing the oncological characteristics, surgical safety, and prognosis of the two groups of patients. Then, Fisher's exact, Chi-square tests and Mann–Whitney U test were used to conduct statistical analysis on the demographic characteristics, basic preoperative profile, preoperative HIV treatment, perioperative serological indicators, surgical outcomes, oncological characteristics, and survival of the two groups of patients.

Research results

Compared to patients without HIV, patients with HIV are more reluctant to receive chemotherapy, and they had fewer preoperative and postoperative leukocytes, fewer preoperative lymphocytes, lower carcinoembryonic antigen levels, more intraoperative

bleeding, more metastatic lymph nodes, higher node stage, higher tumor node metastasis stage, shorter overall survival, and shorter progression-free survival. The willingness and appropriate treatments of patients with HIV and CRC need more attention.

Research conclusions

Compared to patients with CRC and without HIV, those with HIV with the same tumor stage and tumor site have a higher number of lymph node metastases and worse postoperative long-term survival, however, the risk of surgery is not increased.

Research perspectives

The reasons why fewer patients with HIV and colorectal cancer receive chemotherapy need to be discovered and addressed. Appropriate treatments for them should be developed as soon as possible.

ACKNOWLEDGEMENTS

The authors are grateful to all their colleagues who helped prepare this article. We thank Yi Xiao for his diligence in data entry. The authors have not applied any AI tools.

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