ORIGINAL SCIENTIFIC REPORT

Outcomes Following Major Oncologic Operations for Non-AIDS-Defining Cancers in the HIV Population: A Matched Comparison to the General Population

Amber Chi[1] · Bryan E. Adams[2] · Joanna Sesti[1] · Subroto Paul[1] · Amber L. Turner[1] ·
David August[1,3] · Darren Carpizo[1,3] · Timothy Kennedy[1,3] · Miral Grandhi[1,3] ·
H. Richard Alexander[1,3] · Steven K. Libutti[3] · Stuart Geffner[1] · Russell C. Langan[1,3]

Abstract

Introduction Human immunodeficiency virus (HIV) patients are living longer due to the availability of antiretroviral therapies, and non-AIDS-defining cancers are becoming more prevalent in this patient population. A paucity of data remains on post-operative outcomes following resection of non-AIDS-defining cancers in the HIV population.

Methods The National Inpatient Sample was utilized to identify patients who underwent surgical resection for malignancy from 2005 to 2015 (HIV, $N = 52,742$; non-HIV, $N = 11,885,184$). Complications were categorized by international classification of disease (ICD)-9 diagnosis codes. Cohorts were matched on insurance, household income, zip code and urban/rural setting. Logistic regression assessed whether HIV was an independent predictor of post-operative complications.

Results Descriptive statistics found HIV patients to have an increased rate of complications following select oncologic surgical resections. Univariate and multivariate logistic regression found HIV to only be an independent predictor of complications following pulmonary lobectomy ($p = 0.011$; OR 2.93, 95% CI 1.29–6.73). Length of stay was statistically longer following colectomy (2.61 days, 95% CI 1.98–3.44) in those with HIV.

Conclusions Our findings are hypothesis generating and highlight the potential safety of major cancer surgery in the HIV population. However, care providers need be cognizant of the potential increased risk of post-operative complications following pulmonary lobectomy and the potential for increased length of stay. These findings are an initial insight into quality of care and outcomes metrics on HIV patients undergoing major cancer operations.

Introduction

Human immunodeficiency virus (HIV) is a global health problem which has caused over 34 million deaths since the virus was first identified in the early 1980s. Currently, 1.2 million people in the USA are living with HIV, and an estimated 50,000 new infections occur each year [1]. Since 1996, the availability of combination antiretroviral therapy to suppress the virus has allowed more people with HIV to live healthier and longer lives [2, 3]. By mid-2015, over 15 million people worldwide were receiving these medications and in turn between 2000 and 2015, new HIV infections decreased worldwide by 35% and HIV-related deaths decreased by 24% [1, 4].

These improvements in care have begun to transform HIV from a rapidly fatal illness to a chronic condition—leading, in turn, to the growth of an aging HIV-positive population. By 2020, it is expected that the majority of people with HIV in the USA will be aged 50 years or

✉ Russell C. Langan
russell.langan@rwjbh.org

1 Department of Surgery, Saint Barnabas Medical Center, RWJBarnabas Health, Livingston, NJ, USA

2 Department of Mathematical Sciences, United States Military Academy, West Point, NY, USA

3 Division of Surgical Oncology, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA

older—compared with 2009, when only one-third of people with HIV were over 50 years of age [5]. HIV-infected patients now have life expectancies approaching that of the general population [2, 6]. As a result, the development of non-AIDS-defining malignancies is more common, and non-AIDS-defining malignancies are reported to be the second most common cause of death behind AIDS-related complications [7, 8].

Since individuals infected with HIV are living longer, non-AIDS-defining cancers are becoming more prevalent and interest in this area is rising [9]. Traditionally, literature has focused on AIDS-defining neoplasms such as Kaposi's sarcoma, non-Hodgkin's lymphoma and cervical cancer, since they denote the definition of AIDS on account of their occurrence at higher than background rates in patients with HIV [10]. Current literature has identified increased incidence rates for a wide range of malignancies in those infected with HIV [10–13]. Moreover, reports have also suggested inferior median, overall and cancer-specific survival rates for HIV-infected cancer patients as compared to the general population [11, 14, 15].

However, there remains a paucity of data regarding surgical outcomes for HIV patients undergoing procedures for cancer. We therefore sought to assess potential differences in short-term operative outcomes following gastrectomy, pancreatectomy, hepatectomy, colectomy and pulmonary resection for malignancy utilizing a national dataset. HIV-infected and non-infected patient cohorts were matched on type of insurance, household income, zip code and urban/rural setting. We hypothesized that HIV-infected patients would have a significant increase in post-operative complications and length of stay as compared to the general population.

Materials and methods

Data source

We obtained discharge data from the National Inpatient Sample (NIS) from 2005 to 2015. Unweighted patient characteristics are depicted in Table 1. The NIS database is a part of Healthcare Cost and Utilization Project, Agency for Healthcare Research and Quality. NIS contains all the discharges from a stratified 20% sample of all nonfederal community hospitals in the USA, regardless of type or status of insurance. The NIS is the largest all-payer inpatient care database in the USA, containing data on more than 7 million hospital stays. This analysis conducted took into account the sample trend weights and stratification to ensure inferences determined from the sample data are applicable to the population. Following weighted averaging, there were a total of 11,937,926 "patients" included in

the analysis, with 52,742 "patients" infected with HIV. Weighted averages included 282,013 gastrectomies including 1085 HIV patients, 867,182 pancreatectomies including 2915 HIV patients, 750,120 hepatectomies including 10,131 HIV patients, 4.1 million colectomies including 11,524 HIV patients and 6 million pulmonary resections including 27,087 HIV patients using the *International Classification of Diseases, 9th Revision,* primary procedure codes ("Appendix 1"). Procedures which did not have adequate sample sizes to obtain clinically relevant statistical analysis (esophagectomy, pancreaticoduodenectomy, rectal resection) were excluded from the analysis. An IRB waiver was obtained.

Variables of interests

Our primary outcome variables were post-operative complications and length of stay. Post-operative complications were categorized by code on the discharge record via *International Classification of Diseases, 9th Revision,* diagnosis codes ("Appendix 2"). Complications included gastrointestinal, infectious, malnutrition, wound complications, genitourinary, vascular, pulmonary, cardiac, pain, fever, neurologic and other, as well as mortality.

Covariates

Information on patients' sex, age, race, geographical region and primary insurance was extracted from the discharge records. The HIV and non-HIV cohorts were matched on type of insurance, household income, zip code and urban/rural setting.

Statistical analysis

The package "tidyverse" in the software program R was used to filter patients from NIS that underwent esophagectomy, gastrectomy, hepatectomy, pancreatectomy, colectomy or pulmonary resection for malignancy and to classify them as HIV or non-HIV from 2005 to 2015. The final unweighted sample numbers from 2005 to 20015 NIS are provided in Table 1. Utilizing the R package, logistic regression was used to determine if a patient was more likely to encounter complications or death as a result of the surgery if they were HIV positive and Poisson regression used to determine if a patient was more likely to encounter longer post-operative hospital stays if they were HIV positive. Logistic regression took into account the sample weights and stratification provided by NIS to ensure inferences determined from the sample data are applicable to the population. Each initial model was controlled for type of insurance, household income, zip code and urban/rural setting.

Table 1 Characteristics of HIV-infected and HIV-uninfected patients with cancer, 2005–2015 (Unweighted)

Characteristic	HIV-uninfected patients no. (%)	HIV-infected patients no. (%)
Total	241,770	437
Age at surgery		
18–44	10,882 (4%)	41 (9%)
45–54	28,143 (12%)	180 (41%)
> 55	202,262 (84%)	216 (50%)
Sex		
Male	120,288 (50%)	324 (74%)
Female	121,235 (50%)	113 (26%)
Race		
White	154,745 (66%)	147 (34%)
Black	22,036 (9%)	192 (44%)
Hispanic	14,569 (6%)	42 (10%)
Other	5229 (2%)	19 (5%)
Unknown	37,261 (16%)	35 (7%)
Payer information		
Medicare	142,695 (59%)	148 (34%)
Medicaid	12,736 (6%)	120 (28%)
Private including HMO	75,091 (31%)	128 (30%)
Self-pay	5511 (2%)	18 (4%)
Other	4664 (2%)	19 (4%)
Location of the patient		
Central counties of metro areas ≥ 1 million	50,779 (22%)	121 (28%)
Fringe counties of metro areas ≥ 1 million	43,935 (19%)	71 (16%)
Counties in metro areas of 250,000–999,999	34,501 (15%)	56 (13%)
Counties in metro areas of 50,000–249,000	16,386 (8%)	15 (4%)
Micropolitan counties	20,812 (10%)	11 (3%)
Unknown	61,471 (26%)	158 (36%)
Year		
2005–2007	85,618 (35%)	125 (29%)
2008–2010	62,912 (26%)	113 (26%)
2011–2013	60,250 (25%)	128 (30%)
2014–2015	32,990 (14%)	71 (16%)
Cancer type		
Liver	6171 (3%)	65 (15%)
Colon	180,592 (75%)	251 (60%)
Lung	20,593 (9%)	40 (9%)
Pancreas	16,321 (7%)	28 (6%)
Stomach	13,378 (6%)	38 (9%)

Results

The final weighted cohort consisted of 52,742 HIV-infected patients and 11,885,184 HIV-uninfected patients (Table 2). Based on previously described matched cohorts, initial descriptive statistics found that that HIV-infected patients had an increased rate of complications following colectomy, hepatic lobectomy, pulmonary resection (segmental and lobe), gastrectomy and distal pancreatectomy.

There were no observed differences between cohorts in post-operative mortality.

Univariate analysis

Post-operative complications

On univariate analysis, HIV infection was identified as a positive predictor of increased post-operative

Table 2 Disease sites and weighted number of patients in each cohort and procedure performed.

Disease site and weighted number of patients	Procedure performed
Colon	Laparoscopic right hemicolectomy
Non-HIV	Laparoscopic left hemicolectomy
$N = 4.1$ million	Laparoscopic sigmoidectomy
HIV	Open sigmoidectomy
$N = 11,524$	Open cecectomy
	Open transverse colectomy
Liver	Lobectomy of liver
Non-HIV	
$N = 739,989$	
HIV	
$N = 10,131$	
Lung	Segmental resection of lung
Non-HIV	Lobectomy of lung
$N = 6$ million	
HIV	
$N = 27,087$	
Stomach	Partial gastrectomy with anastomosis to esophagus
Non-HIV	
$N = 280,928$	Partial gastrectomy with anastomosis to duodenum
HIV	Open partial gastrectomy
$N = 1,085$	
	Total gastrectomy
Pancreas	Distal pancreatectomy
Non-HIV	
$N = 864,267$	
HIV	
$N = 2,915$	

complications following pulmonary lobectomy ($p = 0.011$). However, there was no difference observed between cohorts following pulmonary segmental resection, hepatic lobectomy, distal pancreatectomy, partial or total gastrectomy or colectomy (Table 3).

Length of stay

In those with HIV, post-operative length of stay was found to be increased on univariate analysis following pulmonary segmentectomy ($p = 0.0014$), hepatic lobectomy (< 0.0001), and colectomy ($p < 0.001$). (Table 4).

Multivariate analysis

Post-operative complications

On multivariate logistic regression analysis, HIV remained as a positive predictor of increased post-operative complications following pulmonary lobectomy. In keeping with

the univariate results, HIV was not associated with an increase in complications following pulmonary segmental resection, hepatic lobectomy, distal pancreatectomy, partial or total gastrectomy or colectomy (Table 3).

Length of stay

Following multivariate analysis, HIV only remained a positive predictor of increased length of stay following colectomy (OR 2.61, 95% CI 1.98–3.44) (Table 4).

Discussion

Since the introduction of highly active antiretroviral therapies (HAART), HIV patients are living longer and due to this, we are seeing a change in cancer incidence rates. [16]. The number of AIDS-defining malignancies have decreased while the number of non-AIDS-defining cancers has steadily increased [16]. Currently, cancer is the second leading cause of non-AIDS death in HIV-infected individuals [14]. Although there have been reports assessing medical oncology outcomes, there is little to no data published on surgical oncology outcomes in the HIV population. We therefore sought to assess whether differences existed in the surgical population. We hypothesized that HIV-infected patients undergoing major cancer surgery would have a statistically significant increase in post-operative complications. However, our current study found HIV was only associated with an increase in post-operative complications following pulmonary lobectomy.

Although this is a hypothesis generating study with great bias, we believe our results highlight the potential for relative safety following major cancer surgery in the HIV population. To date, there remains a paucity of data on post-operative outcomes following major surgery in the HIV population. However, a retrospective cohort study at Johns Hopkins reported an increased mortality in HIV-infected non-small cell lung cancer (NSCLC) patients matched to HIV-uninfected patients (hazard ratio 3.08, 95% CI 1.85–5.13) [17] . In agreement, Suneja et al. [18] examined the Texas Cancer Registry and concluded that HIV infection was associated with higher lung cancer-specific mortality (hazard ratio 1.34, 95% CI 1.15–1.56) adjusted for demographics and tumor characteristics. In this analysis they found that HIV-infected NSCLC patients were less frequently treated for lung cancer than non-HIV-infected patients and this may have affected survival [18]. On the contrary, Rengan et al. [19] utilized the Surveillance, Epidemiology and End Results (SEER) registry and examined patients with NSCLC and found that HIV-infected patients with stage I or II disease who underwent surgical resection had no significant difference in median

Table 3 Logistic regression assessing HIV as a coefficient for predicting post-operative complications

Cancer	Procedure	Univariate regression	Multivariate regression	
		p value	OR	95% CI
HIV as positive predictor				
Lung	Lobectomy	0.011	2.93	1.29–6.73
HIV non-predictor				
Lung	Segment resection	0.650	1.42	0.32–6.36
Liver	Hepatic lobectomy	0.879	1.08	0.39–3.06
Pancreas	Distal pancreatectomy	0.874	1.16	0.19–6.93
Stomach	Partial gastrectomy	0.282	3.33	0.37–29.91
	Total gastrectomy	0.871	1.15	0.21–6.30
Colon	Laparoscopic sigmoidectomy	0.952	1.04	0.33–3.22
	Open sigmoidectomy	0.523	1.25	0.63–2.49
	Open cecectomy	0.358	2.74	0.32–23.49
	Open transverse colectomy	0.269	2.06	0.57–7.39

Table 4 Univariate and multivariate analysis depicting procedures which HIV statistically impacted post-operative length of stay

Cancer	Procedure	Univariate analysis	Multivariate regression	
		p value	OR	95% CI
Lung	Pulmonary segmentectomy	0.0014	NS	NS
Liver	Hepatic Lobectomy	< 0.0001	NS	NS
Stomach	Partial Gastrectomy	0.0582	NS	NS
Colon	Sigmoidectomy	< 0.0001	2.61	(1.98, 3.44)

NS not significant

survival compared to the HIV-uninfected cohort (50 months vs. 58 months, $p = 0.88$). Similarly, Montoto et al analyzed oncologic outcomes in HIV and non-HIV patients with classical Hodgkin lymphoma and found that HIV status was not associated with outcome differences in the era of HAART therapy [20]. We believe these results point toward more broad healthcare disparities rather than biological differences in outcomes. With respect to our surgical data, we believe we may have mitigated some disparities through matching our cohorts on type of insurance, household income, zip code and urban/rural setting.

Interestingly, a recent survey of US medical and radiation oncologists looked to identify provider practice patterns and found that less than 80% of providers stated they would offer standard cancer therapy to HIV-infected patients, with 70% responders noting insufficient guidelines were available to aid decision making [21]. In brief, there are few cancer treatment guidelines specific to HIV-infected patients and many physicians lack experience in treating HIV-infected patients with cancer. One potential reason for this observation is a difference in cancer treatment [14]. Numerous reports have identified cancer care disparities in the HIV-infected population and have hypothesized that the outcome differences are related to

these treatment disparities and not the HIV viral infection. Suneja et al. [22] conducted a large, population-based study which examined patients from three US states who had one of several commonly diagnosed cancers and found significant differences in cancer treatment rates between HIV and non-HIV-infected patients. This group then validated this analysis utilizing the National Cancer Database (NCDB) and found that HIV-infected patients with cancer were less likely to receive cancer treatment regardless of insurance status and comorbidities [16]. Overall, HIV status was associated with a lack of standard treatment modality in the studied population [16]. Moreover, Coghill et al. [23] published a study evaluating the excess mortality of HIV-infected patients and found that overall mortality in patients with HIV and cancer was significantly higher than the summation of mortality rates based on HIV and cancer separately. We therefore hope that our analysis bolsters further study into this topic with an overall goal of improving the current healthcare disparities which seem to be driving oncologic results for HIV patients.

There are several important limitations to our study. Clearly there is inherent bias with a national retrospective database. First, we did not have data regarding HIV severity, CD4 counts or receipt of antiretroviral therapy.

Second, our results are an extrapolation to the US population since data were created based on a weighted analysis of a retrospective database. Also, there may be a patient selection bias since we do not have morbidity status. The HIV patients assessed in this study may be a highly selected group of patients to have undergone major cancer operations. We also note that the sample size for certain cancers or cases were low which may have influenced outcomes. We recognize that these results should not solely be used to establish stringent guidelines for providing oncologic surgical care for HIV patients. We therefore present our results as hypothesis generating, rather than definitive or practice changing. Also, it should be noted that these results may not be accurate or able for implementation to the HIV populations within the African continent, which encompasses 70% of the world's HIV population. Despite these limitations, this study did encompass a large patient population using a national representative dataset. Moreover, we believe we are filling a knowledge gap since we believe this is the first analysis to focus on the surgical aspects of cancer care for those infected with HIV in the USA.

The results of the current study indicate that cancer surgery within the HIV population in the USA has the potential to be safe. Although our population may be a highly selected one, our regression analysis only found HIV status to increase post-operative complications following pulmonary lobectomy and length of stay was minimally increased following colectomy. Our findings suggest that HIV status should not exclusively be used to prohibit oncologic resections and the surgeon must assess many other factors to determine the safety and feasibility of tumor extirpation in this patient population. However, care providers need to be cognizant of the potential increased risk of post-operative complications following pulmonary lobectomy. These findings are an initial insight into quality of care and outcomes metrics on HIV patients undergoing major cancer operations and serve as a platform to assess whether HIV impacts other aspects of the continuum of care. Future analysis is planned to assess disparities in access to surgical care for those with HIV.

Compliance with ethical standards

Appendix 1: Type of procedures with statistically increased complication rates

	Code and procedure
Colon Non-HIV-4.1 million HIV-11,524	17.33—Laparoscopic right hemicolectomy 17.35—Laparoscopic left hemicolectomy 17.36—Laparoscopic sigmoidectomy 45.76—Open sigmoidectomy 45.72—Open cecectomy 45.74—Open transverse colectomy
Liver Non-HIV-739,989 HIV-10,131	50.3—Lobectomy of liver
Lung Non-HIV-6 million HIV-27,087	32.3—Segmental resection of lung 32.4—Lobectomy of lung
Stomach Non-HIV-280,928 HIV-1085	43.5—Partial gastrectomy with anastomosis to esophagus 43.6—Partial gastrectomy with anastomosis to duodenum 43.89—Open partial gastrectomy 43.99—Total gastrectomy
Pancreas Non-HIV-864,267 HIV-2915	52.52—distal pancreatectomy

Appendix 2: ICD-9 comorbidity, procedure and complications codes used for data collection

	ICD-9 code
Cancer diagnoses	Esophagus: 150.0, 150.1, 150.2, 150.3, 150.4, 150.5, 150.6, 150.7, 150.8, 150.9
	Stomach: 151.0, 151.1, 151.2, 151.3, 151.4, 151.5, 151.6, 151.8, 151.9
	Colon: 153.0, 153.1, 153. 2, 153. 3, 153. 4, 153. 5, 153.6, 153.7, 153.8, 153.9
	Rectum: 154.0, 154.1, 154.2, 154.3, 154.8
	Pancreas: 157.0, 157.1, 157.2, 157.3, 157.4, 157.8, 157.9
	Liver: 155.0, 155.1, 156.1
	Lung: 162.0, 162.2, 162.3, 162.4, 162.5, 162.8, 162.9
Procedures	Colorectal: 45.4, 45.5, 45.7, 45.8, 45.9, 46.0, 46.1, 46.2, 48.4, 48.5, 48.6, 48.9
	Esophageal: 42.4, 42.5, 42.6
	Gastric: 43.5, 43.6, 43.7, 43.9
	Hepatobiliary: 50.3, 50.4, 51.39, 52.5, 52.6, 52.7
	Lung: 32.3, 32.4, 32.5
	Pancreatic: 52.0, 52.5, 52.6, 52.7
Comorbidities	305.1, 786.0, V46.0, 491.21, 789.5, 401.9, V45.11, 199.0, 879.8, V58.65, 783.21, 289.9, 286.9, 414.01, 250.03, 250.10, 428.0, 244.8, 276.9, 280.0, 285.9, 443.9, 571, 571.0, 571.1, 571.3, 571.4, 571.5, 571.6, 571.8, 571.9, 572.8, 585.9, 584.9, 042, 070.70, 278.00, 305.00, 305.90, 285.9, 311.0, 435.9, V12.54, 437.0, 438.14, 456.1, 456.2, 410.9, 440.22, 342.9, 344.1, 99.0, V58.2, 285.3, V58.11, 990.0, V58.0, 995.91
Mortality	042, 043, 044, 001, 002, 003, 005, 020, 021, 022, 023, 024, 025, 026, 027, 028, 029, 030, 031, 032, 035, 037, 039, 040, 041, 046, 047, 048, 049, 050, 051, 052, 053, 054, 056, 057, 058,0 59, 060, 061, 062, 063, 064, 065, 066, 067, 068, 069, 070, 071, 072, 073, 074, 075, 076, 077, 078, 079, 080, 081, 082, 083, 084, 085, 086, 087, 088, 097, 098, 099, 100, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 139
	998.9

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