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Research Article

Pathologic Factors Affecting Colorectal Cancer Survival in a Jamaican Population - The UHWI Experience

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Abstract

Background: Colorectal carcinoma (CRC) is the third most common cancer and a leading cause of cancer-related deaths in Jamaica. Globally, CRC mortality rates have been decreasing in developed countries however CRC mortality rates are trending upwards in low-income or developing countries.

Objective: To estimate the overall five-year survival, and to determine the pathologic factors associated with overall survival of colorectal adenocarcinoma after surgery at the University Hospital of the West Indies (UHWI).

Design: Retrospective, observational (cross-sectional) study.

Settings: UHWI, Mona, Kingston, Jamaica.

Patients: 217 patients who underwent operative resection of colorectal adenocarcinoma from January 2004 to December 2013.

Main Outcome Measures: Summarizes and analyzes demographic, clinical data, histopathological data and survival rates. Single predictor Cox regression models were used to establish associations between survival and specified clinicopathological characteristics.

Results: Median survival time post therapeutic intervention was 48 months. Late stage at diagnosis, positive circumferential resection margins, neural and vascular invasion as well as three or more nodal metastases were all associated with significantly worsened outcome.

Conclusions: Despite surgical quality meeting USA standards, CRC survival rates in Jamaica are 13% lower than survival of CRC in Non-Hispanic Blacks in the USA. The survival trends found by our study support the application of international indices for CRC prognostication to Jamaican patients.

Keywords: *Colorectal Carcinoma (CRC); University Hospital of the West Indies (UHWI)*

Introduction

Colorectal carcinoma (CRC) is the third most common cancer and a leading cause of cancer-related deaths in Jamaica [1]. Globally, CRC mortality rates have been decreasing in developed countries while in contrast CRC mortality rates in countries with more limited resources have been trending upwards [2]. The incidence of CRC, regardless of gender, has been increasing in the Jamaican population as most recently reported by Gibson., *et al.* in 2007 [1]. According to the WHO Mortality database, 113 persons died of colorectal and anal malignancies in Jamaica in the year 1980. By the year 2011, the annual CRC mortality in Jamaica had steadily risen to 290 persons [3]. Considering that, according to World Bank estimates, the population of Jamaica increased by only 23%, from 2.163 million in 1980 to 2.829 million; the doubling of mortality from lower gastrointestinal tract malignancies seems disproportionate [4].

The Caribbean diaspora forms a significant proportion of the immigrant population of many developed countries, especially the United States of America. Of the four million Caribbean immigrants documented in the 2014 U.S. Census Bureau American Community survey, 18% hail from Jamaica [5]. Notably, Jamaicans, though residing in a developed nation, seem to face socioeconomic barriers that hinder access to screening for CRC. Jamaicans and African-Americans (AA) are more likely than Caucasian Americans to have never undergone fecal occult blood testing for CRC screening [6]. It therefore is not surprising that, non-Hispanic Blacks in the USA had the highest incidence of colon cancer mortality (20.5%) of all ethnicities from 2010 - 2014. The average rate of CRC-related mortality for all ethnicities was 14.8% [7].

Since the introduction of Dukes' prognostic classification system 80 years ago, there has been significant progress in the systematic classification of colorectal cancer by stage. The Tumor Node Metastasis (TNM) CRC staging by the American Joint Committee on Cancer (AJCC), is now the most universally applied system. In addition, contemporary enquiry has been focused on other aspects (tumor differentiation, patient age and venous invasion) related to the pathology of colorectal cancer that may impact prognosis [8].

With continued advancement in histopathologic methodology, it has become evident that not all pathologic factors hold the same importance in terms of prognosis. Several pathologic factors have been shown to be associated with survival in various populations worldwide, however to date there are no published data regarding the pathologic factors associated with colorectal cancer survival in the Jamaica nor in any of the English-speaking Caribbean islands. With a population of predominantly African ancestry, it is of great importance to identify exactly which pathologic factors are associated with the prognosis and survival, of colorectal cancer patients in Jamaica. Such descriptors may also be applicable to the considerable Jamaican and African diaspora worldwide.

We thus sought to determine and compare the 5-year overall survival rate for colorectal cancer, firstly as an aggregate, and then with regard to each individual stage of CRC according to the American Joint Committee on Cancer system. We also sought to ascertain the pathologic factors affecting CRC survival and the cure rate of patients at the University Hospital of the West Indies (UHWI). We found that Jamaican CRC cases presented at late stage and CRC survival rates in Jamaica are 13% lower than survival of CRC in Non-Hispanic Blacks in the USA. The data obtained is invaluable in implementing changes to improve colon cancer care in Jamaica and the English-speaking Caribbean and may be extrapolated to the Afro-Caribbean diaspora worldwide.

Materials and Methods

This retrospective, observational study summarizes and analyzes demographic, clinical and histopathological data of patients who underwent operative treatment of colorectal adenocarcinoma at UHWI, Mona, Kingston, Jamaica from January 2004 to December 2013.

The data was collected from the Jamaica Cancer Registry and statistical analysis was conducted using STATA version 12. Results are reported in aggregate form, maintaining patient confidentiality.

UHWI is a Type A teaching hospital and referral center, accepting patients from across Jamaica. Previous studies have estimated that UHWI provides ~49% of CRC resection surgeries in the Jamaica public health care system [10].

All CRC cases entered during the period January 2004 to December 2013 were identified and assessed for inclusion. Only adult patients diagnosed histologically with CRC and receiving definitive management at UHWI were included. Patient cases under the age of 18 years, patients who developed CRC on a background of Inflammatory Bowel Disease, patients operated on at external institutions or having a final histological diagnosis other than CRC were excluded.

Case characteristics are summarized in table 1 and 2 and include patient demographics, gross tumor characteristics such as anatomical location, and histopathological findings.

	Summary n (%)	Logrank Test of Equality of Survival P - value
Age (years)*		0.006**
Mean+ SD	64.8 + 14.3	
Median	65	
Gender		0.056
Female	116 (53.5)	
Male	101 (46.5)	
Location		0.301
Right	89 (41.0)	
Left	24 (11.1)	
Transverse	17 (7.8)	
Rectum	66 (30.4)	
Sigmoid	20 (9.2)	
Surgery		0.184
None	13 (6.0)	
Elective	184 (84.8)	
Emergency	20 (9.2)	
Type of surgery		0.104
Open	189 (87.1)	
Laparoscopic	26 (12.0)	
Anastomosis		0.098
Hand sewn	139 (64.1)	
Stapled	50 (26.7)	
Grade of differentiation		0.482
Poor	17 (7.8)	
Moderate	163 (75.1)	
Well	33 (15.2)	
Perforation		0.079
No	146 (67.3)	
Yes	11 (5.1)	
Grade		0.118
High	6 (2.8)	
Low	109 (50.2)	

Table 1: *Summary of patient characteristics and tumor pathology.*

*** p – value from a single predictor cox regression model.*

Percentages do not sum to 100% due to missing data.

	Summary n (%)	Logrank Test of Equality of Survival P - value
Margins		0.120
Positive	1 (0.5)	
Negative	166 (76.5)	
Circumferential Resection Margins		< 0.001
Uninvolved	162 (74.7)	
Involved	23 (10.6)	
Venous Invasion		0.006
No	111 (51.2)	
Yes	43 (19.8)	
Perineural Invasion		0.026
No	132 (60.3)	
Yes	18 (8.3)	
No. of Positive Nodes		0.024
None	99 (45.6)	
1 - 2	44 (20.3)	
3+	35 (16.1)	
Dukes' Stage		< 0.001
A	24 (11.1)	
B	71 (32.7)	
C	79 (36.4)	
D	17 (7.8)	
TNM Stage		< 0.001
1	26 (12.0)	
2	67 (30.9)	
3	70 (32.3)	
4	23 (10.6)	
Local Resection		0.401
No	163 (75.1)	
Yes	9 (4.2)	
Chemo		0.247
No	95 (43.8)	
Yes	75 (34.6)	

Table 2: *Summary of tumor pathology.*
Percentages do not sum to 100% due to missing data.

Clinical records were used to extract patient status at the end of the evaluation period, December 31, 2015. The time to death was defined as the number of months from surgery until the patient's death. Persons who were not confirmed deceased were censored at the date of their last clinic visit.

The objectives of this study were to estimate the 5-year overall survival and to determine the pathologic factors associated with overall survival of CRC after surgery at UHWI.

Statistics

After data were summarized, single predictor Cox regression models were used to establish associations between survival and numeric characteristics such as patient age. Log rank tests were conducted to determine whether the survival function differed across vari-

ous values of categorical characteristics such as gender and tumor location. Single predictor Cox regression models were then built to estimate crude hazard ratios (HR_C) i.e. the risk of death, while multivariable Cox regression models were built to determine the adjusted hazard ratios (HR_A) for the variables which significantly ($p < 0.05$) predict a person's risk of death. Models were compared using Bayesian Information Criteria (BIC) to determine which was the best predictor of the survival times in the dataset [11]. The goodness of fitness of the final model was tested using the Cox-Snell residuals.

Results

A total of 217 persons met the inclusion criteria for this study. The median survival time was approximately 48 months after surgery (Figure 1). Patient's ages ranged from 27 - 99 years, with a median of 65 years. The odds of achieving 5-year survival post-CRC resection declined significantly with advancing age ($p = 0.006$). There were 116 (53.5%) females and 101 (46.5%) males in the study population. Female gender had a moderate association with enhanced survival ($p = 0.056$).

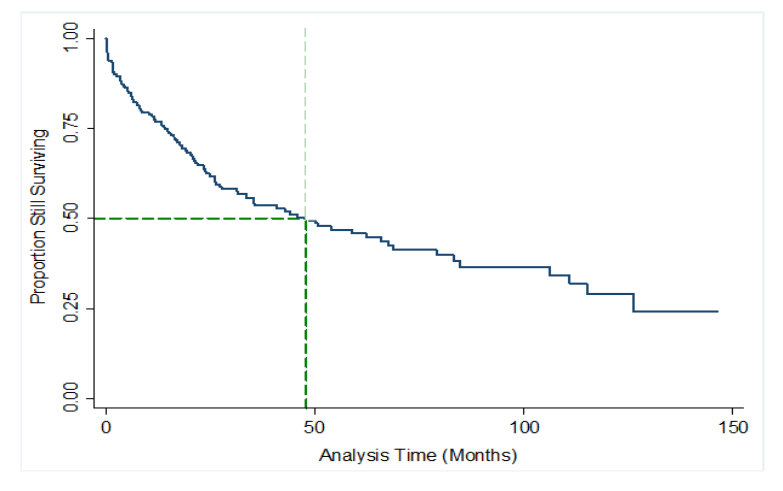

Figure 1: *Kaplan-Meier curve showing survival of the study sample.*

The majority (184, 84.8%) of patients underwent elective surgery, however, this did not confer a statistically significant survival advantage as compared to emergency procedures. The minority (9 or 4.2%) of surgeries performed were simple local resections. Persons undergoing such procedures did not have a significantly enhanced survival. Open laparotomy represented the majority of procedures/resections (87.1% or 189) performed while the remainder were laparoscopic surgeries. The anatomic locations of CRC are summarized in table 1 and we found that the majority of tumors (89, 41.0%) were localized in the right colon. There was no correlation between tumor location and survival. To restore enteric continuity, most (139, 64.1%) anastomoses were hand sewn; this method conferred a moderate survival advantage ($p = 0.098$). At the time of surgery, most (146, 67.3%) cases had no evidence of intestinal perforation at the tumor site but the presence of perforation was moderately ($p = 0.079$) associated with decreased survival time.

Most (163, 75.1%) CRC tumors were moderately differentiated, however the grade of differentiation was not associated with survival time. About half (109, 50.2%) were low grade tumors and tumor grade was not found to significantly impact survival. Most (166, 76.5%) longitudinal resection margins were found to be negative. Most (162, 74.7%) tumors had uninvolved circumferential resection margins (CRM). The presence of involved circumferential resection margins was significantly ($p < 0.001$) associated with decreased survival. Positive longitudinal resection margins were not found to significantly impair survival. Venous invasion was found in 43 (19.8%) resection

specimens and this was significantly associated with decreased survival (p = 0.006). Perineural invasion was noted in 18 (8.3%) resection specimens and this was also significantly associated with decreased survival (p = 0.026). The majority of resection specimens did not contain positive lymph nodes. Negative nodal status was significantly associated with increased survival (p = 0.024). Most cancers (79, 36.4%) were staged as Dukes' C followed by Dukes' B (71, 32.7%). Worsening Dukes' stage was significantly associated with decreased survival. Five-year survival incrementally decreased from 36.0% in Dukes' A to 18.5% in patients with a Dukes' B tumor. No patients with Dukes' D tumors were found alive five years after operative resection. TNM staging placed the majority of tumors at stage 3 (70, 32.3%) or stage 2 (67, 30.9%). Worsening TNM stage was also associated with decreased survival. Table 3 shows the 5-year survival rates by Dukes' staging and TNM staging categories. 46% of patients included in this study were alive 5 years post-surgery. Although a high proportion of patients (95 or 43.8%) reported receiving chemotherapy, systemic oncotherapy did not significantly impact survival rates.

	5 - Year Survival Rate
Overall	45.9%
Duke's Stage	
A	66.0%
B	56.8%
C	47.5%
D	0.0%
TNM Stage	
1	70.9%
2	54.7%
3	47.5%
4	0.0%

Table 3: *Summary of 5-year survival rates by staging.*

Table 4 shows the crude hazard ratios from single predictor Cox regression models. Table 5 shows the adjusted hazard ratios from two different multivariable Cox regression models; one model includes Dukes' staging as a predictor and the other includes TNM staging as a predictor. The final model chosen (Table 5), which included age, circumferential resection margins and Dukes' staging, best predicted patient post-surgery survival time. This model had a higher Bayes' Information Criterion (BIC).

	Single Predictor Models	
	HR_c (95% Conf. Int.)	**P - value**
Age (years)	1.02 (1.01 - 1.04)	0.006
Gender		
Female	1.00 (reference)	0.058
Male	1.44 (0.99 - 2.11)	
Circumferential Resection Margins		
No	1.00 (reference)	
Yes	2.90 (1.66 - 5.07)	< 0.001
Venous Invasion		
No	1.00 (reference)	
Yes	1.97 (1.17 - 3.30)	0.011
Perineural Invasion		

No	1.00 (reference)	
Yes	2.09 (1.08 - 4.04)	0.029
No. of positive nodes		
None	1.00 (reference)	
1 - 2	1.25 (0.71 - 2.19)	0.430
3+	2.07 (1.21 - 3.51)	0.007
Dukes' Stage		
A	1.00 (reference)	
B	1.20 (0.57 - 2.53)	0.622
C	1.66 (0.81 - 3.41)	0.169
D	6.57 (2.79 - 15.48)	< 0.001
TNM Stage		
1	1.00 (reference)	
2	1.66 (0.76 - 3.68)	0.209
3	1.98 (0.91 - 4.33)	0.086
4	7.86 (3.30 - 18.72)	< 0.001

Table 4: *Crude (HR_C) hazard ratios from Cox regression models.*

	Multiple Predictor Model[a]		Multiple Predictor Model[b]	
	HR_C (95% Conf. Int.)	**P - value**	**HR_A (95% Conf. Int.)**	**P - value**
Age (years)	1.03 (1.01 - 1.05)	0.007	1.03 (1.01 - 1.06)	0.001
Circumferential Resection Margins				
No	1.00 (reference)		1.00 (reference)	
Yes	2.27 (1.27 - 4.04)	0.005	2.45 (1.35 - 4.46)	0.003
Duke's Staging				
A	1.00 (reference)			
B	1.12 (0.53 - 2.40)	0.763		
C	1.71 (0.82 - 3.55)	0.151		
D	7.11 (2.84 - 17.84)	< 0.001		
TNM Staging				
1			1.00 (reference)	
2			1.84 (0.81 - 4.19)	0.145
3			2.15 (0.98 - 4.75)	0.056
4			8.82 (3.42 - 22.72)	< 0.001

Table 5: *Adjusted (HR_A) hazard ratios from Cox regression models.*

a: Model included Duke's Staging.

b: Model included TNM Staging.

An increase in age increased the risk of death post-surgery. Patients who had involved circumferential resection margins were twice (HR_A = 2.45) as likely to die post-surgery compared to patients with uninvolved CRM. Patients with Dukes' stage D tumors were 7 times as likely to die post-surgery when compared to patients who had Dukes' stage A.

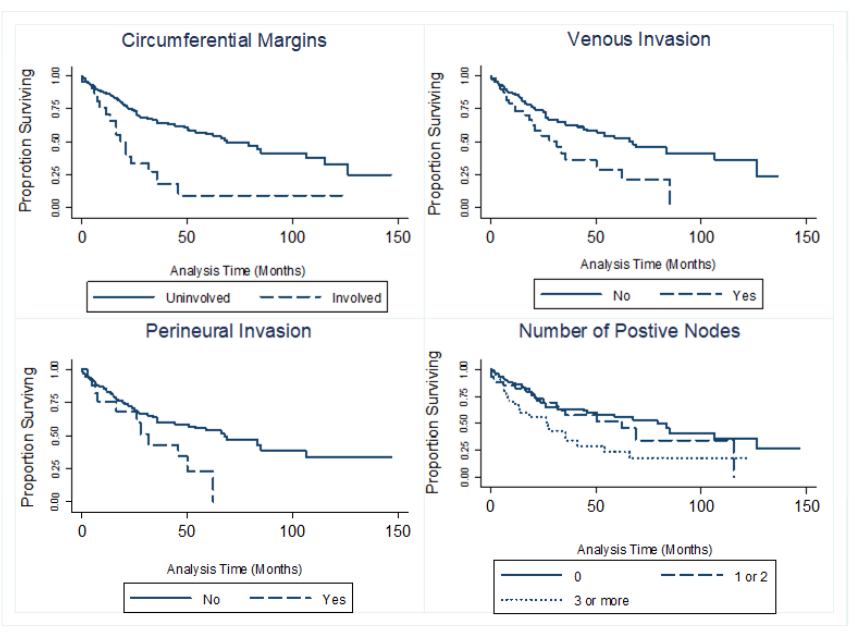

Figure 2: *Kaplan-Meier survival curves by pathology characteristics.*

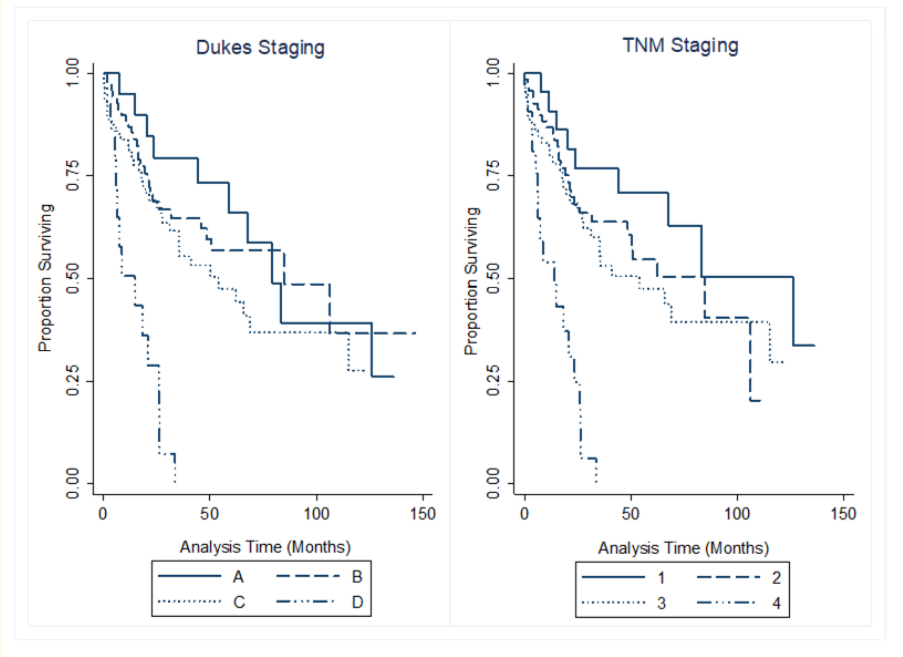

Figure 3: *Kaplan-Meier curves comparing survival across staging protocols.*

Discussion

CRC is the third leading cause of cancer-related mortality in Jamaica. Over the period 1998-2002 a marked rise in the rates of CRC among Jamaican males was noted [1]. Our study demonstrates a 4-year median survival time post therapeutic intervention for CRC at the UHWI, Jamaica during the time period January 2004 to December 2013. Previous studies note a median survival time of 23 months in a cohort of 118 patients with CRC treated across many institutions in Jamaica during the time 2008 - 2012 [12]. Of the 217 cases analyzed in our study, 46% of patients were alive five years following surgery. The previously described cohort enjoyed a similar 5-year survival rate of 33% [12]. However, these numbers both fall drastically below the overall 5-year survival rate (65%) reported for all stages of CRC in the U.S.A. in 2013 [13].

The 5-year relative survival rate for colorectal cancer among Non- Hispanic Blacks in the U.S.A. improved from 45% in 1975-1977 to 59% in 2005-2011 [14]. As a population of predominantly African ancestry, we compared the CRC survival rate for Jamaicans to that of Non-Hispanic Blacks in the USA. Even after accounting for the socioeconomic barriers to CRC care faced by ethnic minorities in the USA, survival in the Jamaican population falls short by 13%. Since surgical quality for CRC at the UHWI consistently meets recommendations of the National Quality Forum [10], it is vital to determine whether intrinsic patient and tumor characteristics in the Jamaican population significantly contribute to this discrepancy in survival compared to developed countries.

The demonstration of increasing all-cause mortality rates with increasing age is not surprising, as with advancing age the rate of co-morbid illness increases. An adjusted Hazard Ratio of 1.03 reflects a small but significant ($p = 0.001$) decreased rate of survival for each additional year of age.

Long term survival of rectal cancer globally decreases if malignant infiltration of the circumferential resection margin is found in the surgical specimen, presumably due to residual tumor at the site of operation [16]. Our results support the application of this principle to Jamaican CRC patients with a 2.90 crude Hazard Ratio for decreased survival ($p = < 0.001$) and a 2.45 adjusted Hazard Ratio ($p = 0.003$).

TNM classification utilizes regional nodal involvement as a major stage determining characteristic. Our study reflected a significant, parallel decrease in survivorship once three or more lymph nodes were involved ($HR_C = 2.07$, $p = 0.007$) or TNM stage 4 was assigned (HR_C 7.86, $p < 0.001$). This is in keeping with international trends [17]. Randomized control trials support an inverse relationship between the ratio of total positive lymph nodes to examined lymph nodes and five-year survival of CRC [18]. However, later meta-analyses suggest no prognostic value of such lymph node ratios [19]. Nevertheless, the U.S. based National Quality Forum recommends that a minimum of 12 lymph nodes be harvested with any CRC resection and the UHWI has been shown to consistently meet that target [10]. Arguably, the removal of more nodes should enhance the accuracy of staging. With more accurate staging should come referral for adjuvant chemotherapy or radiation therapy, which have both been demonstrated to enhance survival in appropriately selected patients.

It also matters precisely which staging algorithm is applied to each patient. Our study revealed a 5% survival advantage in patients staged as TNM 1 versus Dukes' A. However, this study showed an equal survival rate whether patients were staged as TNM 3 or Dukes' C. For patients staged as TNM 2 survival was 2% worse than patients staged as Dukes' B. As per the AJCC 6th edition, TNM 2B previously included T4 whereby the tumor has grown through the entire colon wall, including the serosa and through the peritoneum, as opposed to limited infiltration of the muscularis as specified by the classic version of Dukes' B. This may mean that study patients in the Dukes' B subgroup had a lower extent of local spread as compared to TNM 2C patients, thus accounting for their increased rate of survival.

The Dukes system is rarely used in developed countries for contemporary prognostication. An obvious reason being it lacks the specificity of the TNM stage subgroupings. Revisions of the TNM system, by the AJCC, have been shown to impact survival. When the 6th edition was amended by the AJCC to include more substages as compared to the 5th edition an interesting pattern of survival emerged. Stage 3A colon cancer became associated with statistically significantly better survival than stage 2B. This phenomenon was thought to be due to the fact that stage 3 patients were referred for adjuvant chemotherapy while stage 2 patients were generally not [20].

With the development of AJCC TNM 8th edition in 2017 all disease sites will incorporate non-anatomic prognostic factors for stage grouping, provided a more individualized approach to cancer care. Markers found to significantly decrease survival in our study is venous and perineural invasion by tumour cells. Both factors conferred a two-fold increase in the risk of death. The Jamaican population would likely be best served by this incorporation of other significant prognostic markers, for example to determine the appropriateness of adjuvant chemotherapy in TNM 2 patients on a case by case basis [21].

In resource poor nations such as Jamaica the allocation of public healthcare funds is a matter of life or death for many citizens. A prudent use of funds would be to focus on low cost, high yield primary and secondary prevention methods such as public education and screening. This approach helps the most persons per dollar spent as opposed to the exorbitant individual expenses of chemotherapy and radiation therapy needed in advanced CRC. Early detection of CRC, ideally at the premalignant, readily excised polyp stage, is key in optimizing the use of limited public healthcare funds. Such practice would decrease both CRC related spending per individual, and mortality due to this disease.

In 2017 a survey of CRC screening knowledge and attitudes of the Jamaican populace and the physicians serving them was conducted on 324 lay persons and 57 physicians. Although 98% of physicians agreed that CRC screening was important, only 58% indicated occasionally offering same to their patients, while 21% admitted to never offering their patients screening. Conversely, only 17% of lay persons believed they knew enough about CRC screening on their own [22].

This knowledge gap and insufficiency of communication can be addressed at the level of the public health care system. A French randomized control trial determined that when General Practitioners caring for adults at average risk of CRC were given with a list of their patients who were not up-to-date with their CRC screening, it resulted in a small but significant increase in patient participation in inexpensive FIT screening at 1 year compared with patients who received usual care [23]. A U.S. based program with 5999 enrollees receiving mailed outreach invitations to undergo FIT or colonoscopy resulted in a 27.7% ($p < 0.001$) increase in the rate of CRC screening completion over the ensuing three-year period, versus usual care. Such interventions should not be cost prohibitive to explore and are highly likely to be efficacious in Jamaica.

Our study faced a number of limitations, largely due to the retrospective nature of data collection. The patient records examined were handwritten hand by differing individuals. This meant that for some cases varying clinical and histopathological data were not derived from the notes. The pathology reports themselves were also not standardized and varied in terminology according to pathologist. While it may be reasonably assumed that the majority of patients in this study were of African extraction, many notes did not specify the ethnic origin of the individual and this data would be useful for further risk stratification. Universal inclusion of a preoperative Carcinoembryonic Antigen (CEA) level would also have been useful for analysis.

Conclusion

Generally, the survival trends found by our study support the application of international indices for CRC prognostication to Jamaican patients. In particular, late stage at diagnosis, positive circumferential resection margins, neural and vascular invasion, as well as, three or more nodal metastases were all associated with worsened outcome.

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