Clinical and Pathological Features of Colorectal Cancer in Patients at a Community Hospital in Puerto Rico

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Objective: Colorectal cancer (CRC) is among the most common cancers in Puerto Rico. Few studies have correlated clinical and pathological variables with the overall survival of CRC patients in Puerto Rico. We report the clinical and pathological characteristics of patients who underwent surgical resection at a community hospital in Puerto Rico.

Methods: Demographic and pathological variables of patients who underwent CRC surgery at Hospital del Maestro from 2006 through 2011 were reviewed. Descriptive statistics (mean, range, and frequency) and the Cox proportional hazards model were used to determine the influence of demographic and pathological variables on survival, after adjusting for age.

Results: Two hundred and five CRC pathology reports were reviewed. Adenocarcinoma represented the most common pathology (202/205; 98.5%). Females represented 52% of the population (106/202) while males represented 48% (96/202). The median age was 71 years (30–96). The right colon was the most common site of presentation (49.7%; 100/201). Stage III was the most common stage at presentation. The presence of mucin, perineural or lymphatic invasion and tumor size were not related to decreased survival. Being male, having a higher stage at diagnosis, and having a moderately or poorly differentiated tumor were characteristics related to decreased survival.

Conclusion: This study provides information on clinical and pathological variables and their influence on the overall survival of CRC patients at a community hospital in Puerto Rico. Further research must be performed to identify potential disparities and their influence on the prognosis of this patients. [P R Health Sci J 2014;33:65-70]

Key words: Colorectal cancer, Puerto Rico

In the United States and Puerto Rico, cancer is the second leading cause of death (1). Colorectal cancer (CRC) is one of the most common malignancies in developed countries. In the United States, colorectal cancer is the third most common cancer in incidence and the second leading cause of mortality among men and women; however, both incidence and mortality have declined in recent years (2). In Puerto Rico, colorectal cancer was the second most commonly diagnosed cancer from 2005 through 2009, according to the Puerto Rico Cancer Registry. Approximately 892 males and 789 females were diagnosed with colorectal cancer during that period. Moreover it was one of the leading causes of cancer death, ranking third among males and second among females, in the 5-year period covering 2004 through 2008 (3).

Many studies have been published recently reporting the incidence and prevalence of this disease in people living in Puerto Rico (4-8). However, few studies provide combined information on clinical and pathological data and their influence on the overall survival of colorectal cancer patients. The purpose of this study, then, is to report the clinical and pathological characteristics, as well as survival characteristics, of patients who underwent surgical resection for colorectal cancer at the Hospital del Maestro, a community hospital in the San Juan metropolitan area of Puerto Rico.

Methods

Data source

The study was approved by the Institutional Review Board at the Medical Sciences Campus of the University of Puerto Rico. The pathology reports of all the patients diagnosed with colorectal carcinoma from January 1st, 2006, through December

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31th, 2011, were provided by the Department of Pathology at the Hospital del Maestro.

Study variables

The demographic variables collected were age and sex. The pathological variables obtained included histology, tumor size, location and differentiation, lymph nodes recovered, lymph nodes involved with disease, the presence of lymphovascular invasion, the presence of perineural invasion, mucin production by the tumor, and stage. With respect to tumor location, tumors located from the cecum to the distal transverse colon were classified as right-sided tumors, and those occurring from the splenic flexure to the descending colon were classified as left-sided tumors. Tumors were classified as rectal when they were located within 12 centimeters of the anal verge. Some reports described patients with synchronous tumors. When this occurred, the lesion at the most advanced stage was used for tumor classification. Stage was determined using the TNM classification of the American Joint Committee on Cancer (9). Overall survival was calculated from the date of the pathology report until the date of death (confirmed by the medical record or the Social Security Death Index). For patients alive at the time that the study was performed, overall survival was calculated from the date of the pathology report until the date of the last follow-up visit to the surgeon or medical oncologist.

Statistical analysis

Descriptive statistics using the mean (range) for continuous data were used. Frequency distributions were used for categorical data. Survival of colon cancer was estimated using the Kaplan–Meier method; estimates were categorized by sex, staging, and tumor differentiation. A Cox proportional hazards model was used to assess the influence of the demographic and clinical variables on survival, after adjusting by age. All statistical analysis was performed using the statistical package STATA version 10.1 (College Station, TX, USA).

Results

We obtained the pathology reports of 205 patients with colon cancer, all of whom had their surgery from January 1, 2006, to December 31, 2011. Descriptive demographics and pathological characteristics are shown in Table 1. Histology reveals that 202 out of 205 (98.5%) of the cancers were adenocarcinoma. Two of them were neuroendocrine carcinoma (0.9%) and 1 of them was a medullary carcinoma (0.4%). Given the small number of neuroendocrine and medullary carcinoma histologies, only adenocarcinoma cases were used for the analysis. The mean age of the study participants was 71.2 years (ranging in age from 30–96 years). More than half of the patients were older than 70 years (56.9%). Gender distribution revealed a slightly higher proportion of females over males (52% versus 48%,

respectively). The most common site of tumor location was the right side (49.7%), with the left side being the second most common (42.3%). The rectum was involved in only 5 cases (2.5%). Most of the tumors measured from 2 to 4 centimeters in diameter (45.2%). The pathology reports revealed fewer than 13 lymph nodes per specimen in 76.3% of cases. Most of the reports showed no evidence of lymphovascular invasion (93.6%) or perineural invasion (98.5%). Perineural invasion was seen in cases that had reached stage II, III, or IV. Lymphovascular invasion was most commonly seen in stage III cases (5.45%). About a quarter of the tumors were reported to be mucin-producing (25.4%). Most of the tumors showed moderate or poor differentiation (59.5%). We were able to fully pathologically stage 96% (194/202) of the cases (no lymph node data were available for 8 cases). Stage III was the most common at the time of presentation, followed by stage II, representing 42.8% (83/194) and 32.1% (74/194), respectively.

The Cox proportional hazards model was used to assess the influence of the demographic and pathological variables on overall survival, after adjusting by age (Table 2). Being male was associated with an increased risk of death (HR: 2.08; 95% CI: 1.22, 3.55). Survival curves revealed that 3 year after their surgery, 76.5% of the females were still alive, while only 63.2% of the males were alive at the same time (Figure 1). In addition, a having a tumor at a relatively higher pathological stage was correlated with having a relatively higher risk of death (HR: 2.32; 95% CI: 1.27, 4.27 for stage III. HR: 6.13; 95% CI: 6.13, 2.59, 14.51 for stage IV). At 3 years, only 38.1% of the stage IV patients were still alive, while, in contrast, 64.2% of the patients with stage III tumors had survived to that point (Figure 2). Likewise, tumor differentiation (moderate or poor differentiation) was associated with an increased risk of death (HR: 2.11; 95% CI: 1.17, 3.80). At 3 years, 63.2% of the patients with moderately or poorly differentiated tumors were still alive, in contrast to the 81.7% of patients having well-differentiated tumors (Figure 3), who were not. Tumor size, lymphovascular invasion, perineural invasion, mucin production, and the number of lymph nodes reported were not found to affect survival.

Discussion

To our knowledge this is among the few reports that include combined information on clinical and pathological variables and their influence on the overall survival of colorectal cancer patients living in Puerto Rico. Our retrospective study found that the variables of being a male, having a tumor at an advanced stage at the time of surgery, and having either a moderately or poorly differentiated tumor were all associated with decreased survival.

In Puerto Rico, colorectal cancer is the second most common malignancy among males and females, collectively. For females, colorectal cancer is the second cause of death, while for males it is the third. More importantly, data from the Puerto Rico Cancer

Registry reveals that the incidence rates of colorectal cancer have increased by an average of 1.8% per year for males and 1.5% per year for females during the period of 1987 through 2009. Likewise, cancer mortality rates have increased by an average of 1.7% per year for males and 0.2% per year for females during the same period (3).

Table 1. Description of the demographic and clinical characteristics of the study sample (n = 202)

Characteristics	Frequency	Percent (%)
Age at diagnosis		
(Mean: 71.2; range: 30–96)		
≤ 70 yrs	87	43.1
>70 yrs	115	56.9
Sex		
Female	105	52.0
Male	97	48.0
Stage (n = 194)		
I	22	11.3
II	74	38.1
III	83	42.8
IV	15	7.7
Tumor size (n = 197)		
(Mean: 4.2; range: 0.4-19)		
≤ 2cm	30	15.2
2-4cm	89	45.2
>4cm	78	39.6
LN (n = 194)		
< 12	148	76.3
>12	46	23.7
Lymphovascular invasion		
No	189	93.6
Yes	13	6.4
Lymphovascular invasion		
(by tumor stage) (n = 202)		
Stage I	0	0
Stage II	1	0.5
Stage III	11	5.45
Stage IV	1	0.5
Perineural invasion		
No	199	98.5
Yes	3	1.5
Perineural invasion		
(by tumor stage) (n = 202)		
Stage I	0	0
Stage II	1	0.5
Stage III	2	0.9
Stage IV	0	0
Mucin production (n = 201)		
No	150	74.6
Yes	51	25.4
Tumor differentiation (n = 195)		
Well	79	40.5
Moderate/Poor	116	59.5
Tumor location (n = 201)		
Right (cecum + distal transverse),	100	49.7
Left (splenic flexure + descending colon)	85	42.3
Rectum	5	2.5
Both	1	0.5
Unknown	10	5.0

*Adjusted by age

Several factors affect prognosis and survival in colorectal cancer. Mucinous adenocarcinoma is a subtype of colorectal adenocarcinoma in which more than 50% of the lesion is composed of areas of extracellular mucin (10). Previous reports have observed that mucin-producing adenocarcinomas carry a worse prognosis than that of any other adenocarcinoma, although this observation remains controversial (11-12). The relative seriousness of the prognosis can be attributed to the proximal location of the tumor in question, its stage (that is, it is advanced) at diagnosis, differences in its response to chemotherapy, the presence of microsatellite instability (MSI), and the presence of a BRAF mutation (13-15).

Table 2. Hazard ratios with 95% CI for colon cancer mortality according to demographics and clinical covariates (n=202).

Predictable Variable	HR crude (95% CI)	HR adjusted(95%CI)*
Sex		
Female	1.0	1.0
Male	1.95 (1.15-3.32)	2.08 (1.22-3.55)
Stage		
I/II	1.0	1.0
III	1.98 (1.09-3.60)	2.32 (1.27-4.27)
IV	4.74 (2.04-10.98)	6.13 (2.59-14.51)
Tumor size		
≤ 2cm	1.0	1.0
2-4cm	1.22 (0.52-2.87)	1.20 (0.52-2.83)
>4cm	1.77 (0.77-4.08)	1.83 (0.79-4.22)
Lymph Nodes		
< 13	1.0	1.0
≥13	1.10 (0.59-2.03)	1.22 (0.92-2.89)
Lymphovascular invasion		
No	1.0	1.0
Yes	0.77 (0.24-2.48)	0.80 (0.25-2.57)
Perineural invasion		
No	1.0	1.0
Yes	2.18 (0.53-8.95)	2.40 (0.58-9.95)
Mucin Production		
No	1.0	1.0
Yes	1.05 (0.58-1.88)	0.99 (0.54-1.78)
Tumor Differentiation		
Well	1.0	1.0
Moderate/ Poorly	2.11 (1.17-3.80)	2.11 (1.17-3.80)

*Adjusted by age

A previous report of rectal adenocarcinoma in patients from Puerto Rico showed that those patients with tumors having a mucinous pathology had a tendency toward a decreased overall survival; however, the findings were not statistically significant (7). In our patient population, which included patients with colon and rectal adenocarcinomas, the presence of a mucinous adenocarcinoma had no influence in overall survival.

Several studies have reported that patients with well-differentiated tumors have better survival rates than do patients with poorly differentiated tumors (16-17). In our case series, patients with moderately or poorly differentiated adenocarcinomas had an increased risk of death compared to

patients with well-differentiated tumors, which finding supports those of previous reports.

In our study, being male was related to decreased survival, a phenomenon previously reported by studies in other populations (18-19). The Surveillance, Epidemiology, and End Results (SEER) Program reports an increased incidence of and mortality from colorectal cancer in males (20). In addition, data from the Puerto Rico Cancer Registry confirm that men in Puerto Rico have both a higher incidence and a greater mortality rate of colorectal cancer than women do (3). The reason or reasons for this disparity are unclear since in our database we found no gender differences with respect to age; the tumor stage, size, or differentiation at the time of presentation; or the presence in said tumor of perineural or lymphovascular (or both) invasion. It seems entirely plausible that risk-factor (e.g., obesity) differences or those having to do with hormonal status are responsible for the gender disparities in both incidence and mortality rate.
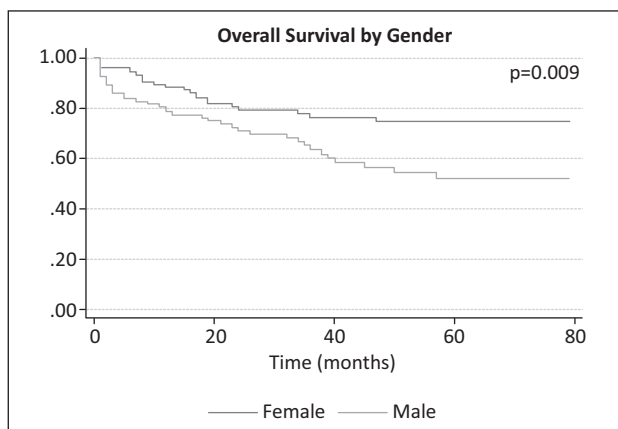

Figure 1. Kaplan-Meier survival curves among CRC cases by gender

Cohort studies have shown that there is an increased risk of colorectal cancer among obese patients. Although that correlation has also been observed in females, studies have also shown that the risk of colorectal cancer remains relatively higher for obese men than it is for obese women (21). In our study we did not have information on the body mass index of our participants, so it is impossible to determine whether either overweight or obesity was a factor related to decreased survival in men.

Some studies have suggested that estrogen has a protective effect against the development of colorectal cancer. Laboratory studies have shown that estrogen controls the growth and differentiation of cells in the gastrointestinal tract (22). Likewise, epidemiological studies have found that menopausal women receiving hormonal therapy are at decreased risk of colorectal cancer (23-24). Most of the women in our study were of menopausal age, however we do

not know whether they were using hormone replacement therapy, so this information will be difficult to evaluate in our population.
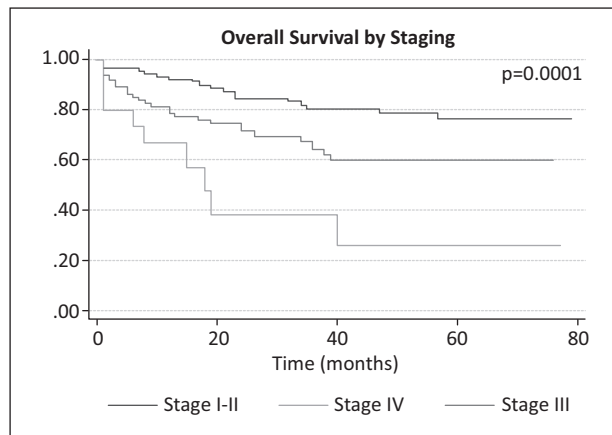

Figure 2. Kaplan-Meier survival curves among CRC cases by stage

The recovery and evaluation of at least 12 lymph nodes has been advised for proper staging and prognostication (25-26). More importantly, studies suggest that adequate lymph node recovery is related to increased survival in colorectal cancer as it allows proper staging and thus the appropriate selection of adjuvant therapy (27). Lymph node recovery is affected by a given patient's comorbidities, the extension of that patient's disease, the surgical complications at the time of surgery (should any exist), the techniques used for tissue preservation, and the expertise of the surgeon and the pathologist (28). Given the retrospective nature of our study, it is impossible to ascertain which of these factors could have affected the lymph node recovery process in our population. Again, in our population of patients, the number of lymph nodes recovered did not have any influence on survival. This finding could be related to the small sample size.
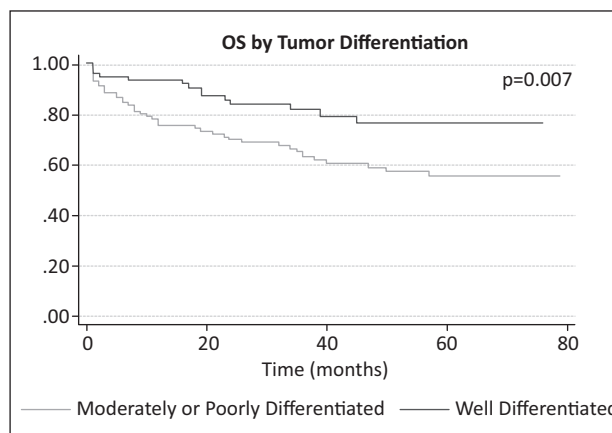

Figure 3. Kaplan-Meier survival curves among CRC cases by tumor differentiation

The presence of either lymphovascular invasion or perineural invasion has been related to a decreased colorectal cancer survival rate in some studies (29). However, those findings remain controversial, and whether the presence of lymphovascular or perineural invasion should be seen as a factor in favor of adjuvant therapy is an area of great debate (30-31). In our population of patients, the presence of neither lymphovascular or perineural invasion influence the survival of CRC patients. It is important to note that we did not have access to any information regarding whether or not any of these patients had in the past undergone or were currently undergoing any kind of adjuvant therapy. Because such therapy would almost inevitably influence survival, this absence of information could be seen as a critical lack.

Having a higher-stage tumor at presentation has been related to a decreased survival rate (19, 31-32). In our population, patients with stage IV tumors had an approximately 6 times greater risk of death than did those patients with tumors that were at either stage I or stage II, thus confirming previous observations (Table 2).

The mean age of our population at diagnosis was 71 years. This is similar to the mean age (69 years) at diagnosis of colorectal cancer patients in Puerto Rico, as reported by the Puerto Rico Cancer Registry (3). A previous report on the population of colorectal cancer patients treated at another community hospital in Puerto Rico revealed that the population at that institution (8) had a mean age of 66 years in the period studied (2002–2004). This difference could be related to the referral pattern of patients, as many of the patients seen at Hospital del Maestro are retired teachers or their spouses.

An important point must be made at this time about colorectal cancer screening. It is unclear whether any of the patients in the study had undergone a screening colonoscopy prior to being diagnosed with cancer. In Puerto Rico, according to the BRFSS, only 28% of the participants had undergone a screening colonoscopy by 1996; by 2010, this number increased to 43% (33). Despite the improvement in the percentage of people undergoing a screening colonoscopy in Puerto Rico, those numbers are still below the Healthy People 2020 target of 70.5% (34). Half of our patients (50.5%) presented with an advanced stage (stage III or stage IV). We certainly cannot conclude that this advanced presentation is related to the lack of appropriate screening. However, the low level of screening and the increase in the incidence and prevalence of colorectal cancer in residents of Puerto Rico are of concern.

Despite the interesting findings of this study, there are several limitations that must be pointed out. First of all this is a retrospective, non-controlled study with a small number of patients. The data were obtained from pathological reports, and those reports do not have information that could have influence the overall survival of the patients such as BMI, high-risk behaviors (smoking), chemotherapies provided and CEA levels at diagnosis. Further studies to describe and evaluate the prognoses and outcomes of Puerto Rican patients with colorectal cancer are warranted.

Resumen

Objetivo: El cáncer colorectal (CCR) es uno de los cánceres más comunes en Puerto Rico. Pocos estudios han correlacionado datos clínicos y patológicos con la sobrevida global de pacientes de cáncer de colon en Puerto Rico. Reportamos las características clínicas y patológicas de pacientes que fueron operados en un hospital de la comunidad en Puerto Rico. Metodología: Se revisaron las variables demográficas y patológicas de pacientes operados de CCR en el Hospital del Maestro durante los años 2006 al 2011. Se utilizaron estadísticas descriptivas (mediana, rango y distribución de frecuencias) y modelos de riesgo proporcional Cox para determinar la influencia de variables clínicas y demográficas en la sobrevida global, ajustada por edad. Resultados: Doscientos cinco reportes patológicos de CCR fueron revisados. El adenocarcinoma representó la patología más común (202/205; 98.5%). Las mujeres representaron el 52% de la población (106/202) mientras que los varones representaron el 48% (96/202). La mediana de edad fue de 71 años (30–96). El colon derecho fue el sitio de presentación más común (49.7%; 100/201). El estadío III fue el estadío de presentación más común. La presencia de mucina, invasión perineural o linfática y el tamaño del tumor no se relacionaron a una sobrevida disminuida. El sexo masculino, tener un estadio alto al diagnostico y tener un tumor moderado o pobremente diferenciado, fueron características que se relacionaron una sobrevida disminuida. Conclusión: Este estudio provee información en las variables clínicas y patológicas y su influencia en la sobrevida global de pacientes de CCR en un hospital de la comunidad en Puerto Rico. Se deben realizar más estudios para identificar potenciales disparidades y su influencia en la prognosis de estos pacientes.

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