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Lagtimes in diagnosis and treatment colorectal cancer:

determinants and association with cancer stage and survival

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Abstract

Background Lagtimes to diagnostic colonoscopy have been used as practice performance measures.

Aim To evaluate the duration, determinants, and outcomes of lagtimes between referral for endoscopic evaluation and colorectal cancer (CRC) diagnosis.

Methods We examined the medical records of 289 patients with CRC and evaluated lagtimes, their potential determinants, and their association with CRC stage at diagnosis as well as overall survival.

Results Median lag between referral and CRC diagnosis was 41 days (41.5% >60 days, 30.1% >90 days). The only significant predictor of lagtime was the initiating event for referral: abnormal symptom, laboratory test, or imaging study was associated with shortest, and presence of family history was associated with longest lag times, respectively. Longer lagtimes were associated with lower mortality risk, but this was completely explained by earlier CRC stage. An analysis restricted to 100 patients referred for abnormal CRC screening tests found no association between duration of lag and CRC stage or mortality.

Conclusions There seems to be no meaningful association between mortality in patients with CRC and lagtimes between referral for colonoscopy and CRC diagnosis for periods up to 2-3 months.

On the contrary, longer lagtimes were inversely associated with CRC stage at the time of diagnosis.

Background

The demand for colonoscopy, both as a screening and diagnostic modality, has increased. Limited endoscopic capacity requires informed decisions on setting priorities for patients

awaiting colonoscopy. Performance measures based on waiting times before obtaining colonoscopy have been proposed. However, very few studies have addressed these lagtimes between referral and CRC diagnosis in US populations in the past decade.

To our knowledge, few studies from the United States have examined the association between type and duration of prediagnosis symptoms with cancer stage or survival. Khubchandani¹ et al. performed a retrospective review of 194 patients diagnosed with non-rectal colon cancer in 1985. Although there were no significant differences in cancer stage among symptomatic patients with different symptom duration (<3, 3-6, 6-12, >12 months), asymptomatic patients had a significantly longer 5-year survival rate. Majumdar et al. looked at delay and outcome (stage) both at the patient and physician level and found that patient delay was much greater than physician delay and that neither had an effect on cancer stage. However, survival was not examined in that study².

Studies conducted outside the United States examined various aspects of lagtimes and their possible effects on outcomes and arrived at inconsistent results. Several studies have not found a significant association between delays and cancer stage and survival [3·4·5·6·7·8]. On the other hand, other studies have found that delays were associated with worse outcomes. For example, in 1965, Rowe-Jones et al.⁹ studied 200 consecutive cases of CRC, 100 of them rectal, in the United Kingdom. Delay, defined as > 2 months between presentation with bowel symptoms and diagnosis, was present in 22% of colon cancer patients. The delayed group had a larger proportion of Duke's C and D cancers. On the other hand, in 1984, UK investigators MacArthur and Smith¹⁰ interviewed 127 of 187 patients with CRC regarding timing of symptoms, doctor visits, and treatment of cancer. This study defined three phases of pretreatment history: time from awareness of symptom to first doctor visit, time from first visit to appointment with a specialist, and time from referral to a specialist to definitive treatment. Median phase 2 delay was 25 days. Median duration from symptoms to treatment was 190 days. Longer delay was associated with more advanced CRC stage at presentation. However, the relationship between delay and outcomes was not examined among patients with similar indications for referral. In 1981, McDermott et al.¹¹ reported that in 624 cases of non-rectal colon cancer in Australia, there were no significant differences in duration of symptoms (< 3, 3-6, 6-12, > 12 months) or type of treatment among groups with different major symptoms. However, survival was significantly longer for patients with symptoms for 3-6, 6-12, or >12 months compared with those with symptoms < 3 months. With these disparate findings, the relationship between lagtime and CRC outcomes is far from clear.

We recently reported a dramatic increase in CRC screening in a VA hospital with non-endoscopic fecal occult blood tests¹² which will likely result in increased requests for and performance of diagnostic colonoscopy. Currently limited endoscopic capacity requires informed decisions to prioritize these requests. Very few studies have addressed the issue of lagtime between referral for endoscopic evaluation and CRC diagnosis in US populations in the past decade; there are none within the VA system. Given renewed interest in CRC detection, it is important to re-examine this issue.

Methods

Study Design

We conducted a retrospective cohort study in patients with newly diagnosed CRC to estimate the lag time between referral and diagnosis of CRC and the lag time between diagnosis and CRC-directed treatment. We examined the potential determinants of these two lag periods and the relationship between duration of either lag period and CRC outcomes,

namely, the stage of CRC at the time of diagnosis and overall survival following CRC diagnosis.

Study Setting

We identified all patients with a new, tissue-based diagnosis of CRC between 1/1/2000 and 6/30/2005 by electronic search based on topography (colon, rectum) and histopathology (adenocarcinoma) in the pathology database at the Michael E. DeBakey VA Medical Center (MEDVAMC). MEDVAMC is one of the largest facilities in the national VA system, serving as the primary healthcare provider for more than 116,000 veterans. We excluded: patients without pre-existing health care at MEDVAMC, defined by at least two outpatient visits or one hospitalization in the year preceding CRC diagnosis; patients diagnosed or treated at other facilities; and patients with pre-existing CRC. Two investigators independently reviewed electronic medical records of patients diagnosed with CRC and determined eligibility for the study.

We collected demographic data (age, race, sex, marital status), clinical features at time of referral (symptoms, abnormal physical findings on abdominal or rectal examination, abnormal screening test, abnormal lab/imaging, presence of family history of CRC as at least one first degree relative with CRC), dates of referral for colonoscopy as documented in the electronic consultation records, CRC diagnosis and CRC-directed treatment, tumor stage at time of CRC diagnosis, and death (if it occurred). Symptoms were determined by documented reports from healthcare providers and included abdominal pain, constipation, blood in stool, melena, weight loss (defined as unintentional 10-lb decline), or change in stool caliber. Abnormal screening was defined a positive fecal occult guaiac based test or polyps seen in flexible sigmoidoscopy in asymptomatic individuals. The following were considered abnormal laboratory values based on reference values reported by the lab: ferritin<11; mean corpuscular volume <81; hemoglobin <=12; hematocrit <36; carcinoembryonic antigen>3 if nonsmoker, >10 if smoker; and albumin<3.4. Date of CRC diagnosis was entered as the date of histologic confirmation of pathology, mostly occurring in the few days following colonoscopic biopsy. Staging information was obtained from intraoperative and histopathologic findings, or in cases of distant metastatic disease, by relevant imaging results; we used the Duke staging system. Date of death (if it occurred) was also collected from medical records through August 2007. Abstracted data were then entered in data collection forms designed in Teleform® (Cardiff, Vista, CA), scanned into a Microsoft Access database, then cleaned and converted into an SAS dataset (SAS Institute, Cary, NC) for analyses.

Analysis

Two lag periods were defined: (1) number of days from referral to CRC diagnosis (date of histopathologic diagnosis), and (2) number of days from date of CRC diagnosis to date of first CRC treatment including endoscopic, surgical, or chemoradiotherapeutic treatment, or end of follow-up in those declining the aforementioned therapies.

We evaluated several potential determinants (demographics, clinical features) and outcomes (CRC stage: stage A, B, C and D; survival) associated with each of the two lag periods. Statistical significance for continuous variables was assessed by parametric tests (Student's *t*-test and analysis of variance) and nonparametric tests (Wilcoxon and Kruskal-Wallis tests). Since the distribution of lag values was highly skewed, these tests were performed on log-transformed values. Linear regression analysis was also used to evaluate these variables.

Univariate and multivariate modeling was used for survival analyses subsequent to CRC diagnosis and modeled by Cox proportional hazards regression. Statistical significance of model predictors was assessed by Wald chi-square tests of the model parameter estimates.

Lastly, to evaluate the effect of lag periods in a relatively homogenous group of patients, we conducted sensitivity analyses in the subset of patients who were diagnosed with CRC subsequent to abnormal CRC screening tests (i.e., positive fecal occult blood test or flexible sigmoidoscopy (polyps) not done in the process of evaluating symptoms or signs).

Results

A total of 635 cases of CRC were identified, of whom 289 patients satisfied the inclusion criteria. The demographic and clinical features of the study population are shown in Table 1. Mean age at time of CRC diagnosis was 68.2 years, and 99.0% were men. Approximately one third were diagnosed following an abnormal CRC screening test. Approximately 76% received either surgical or endoscopic resection, 16% with combined chemoradiotherapy; whereas 8.3% did not receive cancer directed therapy due to early death or refusal of therapy after their diagnosis.

Lag Between Referral and Diagnosis

Determinants—The median lagtime between referral and CRC diagnosis was 41 days (range, 1 to 2063 days). The potential determinants of this lag period are shown in Table 1. The type of initiating event for referral was the sole significant predictor of this lag period ($p=0.005$). The presence of symptoms and abnormal laboratory test or imaging study was associated with a shorter lagtime (34.5 and 37.0 days, respectively) between referral and diagnosis, and the presence of family history (in the absence of symptoms or abnormal screening) was associated with a longer lagtime (187.5 days). For patients whose earliest initiator for referral was an abnormal CRC screening test, the lagtime was 60 days.

There was no association between the lagtime and the presence of several comorbid medical conditions. These included diabetes, hypertension, chronic obstructive pulmonary disease, coronary artery disease, psychiatric disease, and congestive heart failure. In addition, neither race nor marital status was significantly associated with the duration of lagtime between referral and diagnosis.

Outcomes of lag period—We examined the association between the lagtime between referral and CRC diagnosis and CRC stage at time of diagnosis and found a significantly longer lagtime in patients with more advanced stages than those with less advanced stage (Kruskal-Wallis $p = 0.0001$). In Table 2, there is progressive decrease in lagtime with more advanced Duke stage; this relationship was seen for median lag times as well as proportions of patients with lagtimes longer than median interval, 60, and 90 days. We conducted a similar analysis in patients referred because of abnormal screening tests ($n=100$) and found no significant association between lagtime and CRC stage at the time of diagnosis (Table 2). The same findings were observed when we compared stages A and B combined to stage C and D combined (data not shown).

We also examined the association between the lagtime between referral and CRC diagnosis and risk of mortality in a Cox model (Table 3). Longer lagtime was associated with lower mortality risk in the unadjusted analysis (HR=0.61; 95% CI: 0.39-0.96). However, given that the shortest lagtime was associated with symptomatic presentation, likely indicating more advanced CRC stage, the lagtime was no longer associated with mortality in an analysis adjusted for the earliest initiator for referral, stage of CRC at diagnosis, or type of CRC treatment (Table 3). As expected, both endoscopic and surgical resection and less advanced

Duke's stage were associated with a lower mortality risk compared with no treatment or more advanced stage, respectively. Patients in whom CRC was detected by a follow-up test to a previously abnormal CRC screening test had significantly lower risk of mortality compared with patients detected by other methods (HR=0.36; 0.2-0.67). Age was not significantly associated with mortality ($p=0.41$). There were only three women in the study, so gender was not considered in the model. Lastly, patients with right colon cancer had an increased risk of mortality compared with those with rectal cancer, even after adjusting for stage and treatment (HR=3.33; 1.57-7.08).

Similar results were seen when lag between diagnosis and treatment was modeled as a logarithmically transformed continuous variable (Table 4). In this analysis, adjustment for the stage of CRC at diagnosis completely removed the significant effect of lagtime on mortality (i.e., stage explains the effect of lag). A similar, although less profound, explanation was seen when adjusting for CRC treatment.

There was no significant association between CRC stage and lagtime between referral and diagnosis among 100 patients (15 of whom died during the study) who were referred because of abnormal CRC screening test ($p=0.13$). Overall, approximately 63% of CRC was diagnosed in stages A or B.

Lag between diagnosis and treatment—The median lagtime between diagnosis and treatment was 12 days when we included patients with endoscopic treatment (range 0 to 1094 days). Excluding the 79 patients who had no lagtime between diagnosis and treatment because of complete resection during endoscopy, the median lagtime in the remaining 210 patients was 26 days.

Determinants—The lagtime between diagnosis and treatment differed according to cancer site. There were 150 subjects with nonrectal colon cancer that was not resected endoscopically. Of these, 55 had chemotherapy, 126 had surgical resection at some time, and 48 had both. The median time from diagnosis to surgical resection was 15 days and from diagnosis to chemotherapy was 88 days. In 60 subjects with rectal cancer that was not resected endoscopically, 44 had chemoradiotherapy, 42 had surgical resection at some time, and 33 had combined medical and surgical treatment. The median time from diagnosis to chemoradiotherapy was 49 days, whereas the median time from diagnosis to surgical resection was 123 days.

Potential determinants of the lagtime between diagnosis and treatment are shown in Table 5. The lagtime was two-, and three-fold higher in patients with rectal cancers than in those with left or right colon cancers (41 vs. 18 vs. 14 days), respectively.

Outcomes—The lag between diagnosis and treatment was shorter in patients with less advanced compared with those with advanced CRC (the top panel of Table 5) but this was explained by the fact that most patients with Duke stage A were resected endoscopically. Thus, when the analysis is restricted to those who received therapy other than endoscopic resection (the bottom panel of Table 5), there were no significant differences in lagtimes between diagnosis and treatment among groups of patients diagnosed at different Duke stages. The lagtime between diagnosis and treatment was not a significant predictor of mortality ($p=.21$ for Cox PH model; data not shown).

Discussion

In our single-center study, there was a 41-day median lagtime between referral and diagnosis in patients with CRC. The lagtime between referral and diagnosis was actually

inversely related to the tumor stage at diagnosis and to the overall survival. Patients with symptoms, abnormal labs or imaging studies had the shortest lagtime between referral and diagnosis, but also the most advanced cancer stage and shortest survival. The longest survival was found among patients detected because of abnormal CRC screening, mostly fecal occult blood tests. However, even among 100 patients whose cancer was diagnosed in response to abnormal CRC screening, there was no association between duration of lag and cancer stage, or overall survival. In general, the proportions of patients with early (stages A and B) and advanced CRC (stages C and D) remained relatively stable among patients diagnosed within 41 days, 60 days, or 90 days.

The median lag between referral and diagnosis was relatively short from a biological perspective (41 days) and therefore it may not be possible to show differences in mortality based on these lagtimes. However, there was enough variation in that duration to allow the examination of lagtimes of 60 and 90 days. Wong et al. estimated using Markov process to model information obtained for CRC cases diagnosed from a large screening program that the preclinical median duration was approximately 3.1 years for Dukes A and B stages and 1.9 years for Dukes C and D.¹³ These findings further argue against somewhat artificial benchmarks of 30 or 60 days for performing colonoscopy following initial request.

In the current study, the presence of symptoms as the earliest initiator was associated with the shortest lagtime. Several authors have reported an association between the presenting signs or symptoms and the lagtime preceding CRC diagnosis, as well as the stage of cancer at the time of diagnosis. In 1977, Irvin and Greaney³ retrospectively reviewed records of 335 patients with CRC. They found a significantly higher frequency of abdominal pain and multiple symptoms in groups with < 7 months' lagtime between onset of symptoms and first presentation for evaluation compared with those of > 7 months. Although there was slightly more frequent lymph-node metastases and shorter survival in groups with > 7 months delay, this did not reach statistical significance. In another study, Gonzalez-Hermoso et al.⁴ reported in 2004 that, in 660 patients with CRC in Spain, abdominal pain was more frequent in patients with symptom duration < 3 months; and anemia was more frequent in patients with symptoms > 3 months. Unlike our study, there was a statistically significant association between early cancer stage and rectal bleeding ($p<0.001$) or abdominal pain ($p=0.009$). However, our study examined only physician-related delay and did not include delays incurred by patient-related lagtimes.

There was no association between lagtimes in symptomatic patients and long-term survival. While this finding may seem surprising, it is supported by some, but not all, previous studies. A similar study, performed by Mulcahy et al., found that symptom duration was shorter with advanced tumor stage and was shorter for patients presenting with bowel obstruction than those with no or less acute symptoms. Univariate survival analysis showed that long-term survival increased with symptom duration. However, in a multivariate analysis, this effect was mostly accounted for by tumor stage and bowel obstruction.¹⁴ Turunen et al.¹⁵ used a combination of patient interviews and medical record review to evaluate length of delays, delay factors, and stage at diagnosis of 100 consecutive CRC cases in Finland. The median delay was 9.8 months. Patients with severe delay were more likely to have blood in stool and abdominal pain. The most frequent error leading to severe delay was a diagnosis of hemorrhoids, followed by gastroduodenitis, and diverticulosis. The severe-delay group did not differ from the rest of the patients in Duke's classification. Graffner and Olsson⁵ used a 3-month time interval to define patient and doctor delay in 50 patients with rectosigmoid cancer and 50 patients with other colon cancer. Doctor delay was present in 27% of both groups, usually due to neglecting to perform proctoscopy or rectal exam, and in some cases a false negative x-ray; no association between Duke stage and frequency or time of delay was seen. Lastly, Arbmán et al.¹⁶ prospectively studied all CRC

patients from four surgical departments in Sweden over a 2-year period in the mid 1980s. The authors defined a “short delay” as < 1 month total delay, between start of first symptom and diagnosis (patient delay) or date of first presentation to physician to diagnosis (doctor delay). Median patient delays were 0.8 months for colon cancer and 1.5 months for rectal cancer. Median doctor delays were 1.1 months for colon cancer and 0.9 months for rectal cancer. For rectal cancers, a significantly larger proportion of Duke A tumors were seen when the delay was < 1 month. There was no association between duration of delay and stage for colon cancer.

Previous studies have investigated symptomatic presentations that prompt earlier referral or earlier intervention. According to Korsgaard et al., patients with rectal cancer presenting with predominantly rectal bleeding had an associated short diagnostic delay (≤ 60 days) compared with those with other symptoms (change in bowel habits, abdominal pain, constipation or diarrhea) and anemia.¹⁷ Furthermore, rectal bleeding was associated with a decreased relative risk of advanced (Duke C and D) stage. However, in retrospectively analyzing 200 patients with various symptoms in 1979, Holliday et al. found that 100 patients with rectal carcinoma had a mean delay of 38 weeks between onset of symptoms and treatment, compared with 30.5 weeks in 100 patients with colon cancer not involving the rectum.⁷ One explanation to reconcile these differences may reside in the difference in symptoms, where rectal bleeding alone decreases diagnostic time from onset of bleeding to diagnosis. Studies that include rectal cancers presenting as more vague abdominal symptoms may contribute to the longer lag time to diagnosis.

Our findings indicate a longer delay between diagnosis and treatment among patients with rectal cancer than among patients with non-rectal colon cancer. This may be explained by the differences in treatment where rectal cancers treated with neoadjuvant chemotherapy requiring referral to oncology and initial visit prior to first date of chemotherapy or radiation therapy.

Limitations of this study are related to its retrospective nature. The accuracy of onset and type of symptoms are unknown, and is dependent on documentation available for review. However, a trained clinician abstractor verified the CRC diagnosis by procedure and pathology notes; and the dates of death (if any) are virtually complete in the VA records. Our inclusion criteria required two outpatient primary care visits or one prior hospitalization in the year preceding diagnosis, while restrictive, were meant to ensure that patients were adequately followed. The concomitant use of services outside the VA system is possible and may not have been captured by this study. The effect of this missing information (e.g., on CRC treatment) would have exaggerated the amount of lagtime. However, missing information would not have influenced one major outcome, namely, the CRC stage at diagnosis, which was confirmed in all cases. Lastly, it is possible that consults for colonoscopy may be systematically handled in a way that, whether intentionally or not, has affected lagtimes as well as outcomes reported in this study.

The findings also indicate that the longest survival was observed in patients with CRC detected as a result of an abnormal CRC screening test. This is in agreement with previous studies of CRC screening. Symptomatic CRC may be biologically different than CRCs detected by screening, in addition to screening-related differences in patient populations.

However, the lagtime between referral and diagnosis of CRC had no effect on the stage of CRC at time of diagnosis, at least within the 90-day range examined in this study. Since most patients were diagnosed within 90 days, we were not able to examine the effect of longer lagtimes. This finding was also recognized among patients with abnormal CRC screening tests, a group with a rather uniform presentation. The priority of performing

colonoscopy in a “timely” fashion is a subject of intense debate and interest in this group. The findings of this study are not supportive of an empirical time frame, such as 30 or 60 days (or even 90 days). We recommend that such durations, if implemented, be evidence based.

Process-improvement measures such as timely performance of colonoscopy in individuals with abnormal CRC screening tests often make sense because of their own intrinsic value (e.g., rapid reassurance of patients) and because of expected improvement in outcomes such as early detection of cancer, administration of potentially curative therapy, and prolonged survival. However, improvement in outcomes is not surmisable and should be evidence based. Endoscopic manpower is a crucial determinant of success of CRC screening programs. Competing indications for colonoscopy combined with limited endoscopic manpower could result in delayed scheduling of screening and/or diagnostic colonoscopy, which might lead to delay in the discovery of CRC. Attenuating delays for diagnostic colonoscopy may serve as a goal for performance but should be guided by the resultant benefits in survival and treatment measures.

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Table 1
Demographic, clinical features, and potential determinants of lagtime (between referral and diagnosis) of the study population of 289 patients with newly diagnosed first colorectal cancer (CRC) from January 1, 2000, to June 30, 2005, at a single Veterans Affairs Medical Center

	N (%)	Lagtime in days (median)	p Value
Gender			.91
men	286 (99.0%)	42.0	
women	3 (1.0%)	31.0	
Age			.52
40-49	3 (1.0%)	230.0	
50-59	63 (21.8%)	38.0	
60-69	85 (29.4%)	46.0	
70-79	106 (36.7%)	38.5	
80+	32 (11.1%)	52.0	
Marital status			.18
married	151 (52.3%)	48.0	
not married	138 (47.7%)	38.0	
Race			.54
black	86 (29.8%)	42.0	
white	198 (68.5%)	42.0	
other	5 (1.7%)	13.0	
Earliest initiator			.005
symptoms	112 (38.7%)	34.5	
family history of CRC	8 (2.8%)	187.5	
abnormal CRC screening test	100 (34.6%)	60.0	
abnormal lab or imaging	69 (23.9%)	37.0	
Anatomic location			.96
left colon	128 (44.3%)	38.0	
right colon	82 (28.4%)	44.5	
rectum	79 (27.3%)	44.0	
CRC Stage			.0001
A	100 (34.6%)	62.0	
B	83 (28.7%)	41.0	
C	55 (19.0%)	31.0	
D	51 (17.7%)	18.0	
Earliest CRC treatment			.01
none	24 (8.3%)	33.5	
chemotherapy or radiation	46 (15.9%)	21.5	
endoscopic resection	79 (27.3%)	57.0	

	N (%)	Lagtime in days (median)	p Value
surgical resection	140 (48.4%)	40.0	
Coronary artery disease			.25
yes	69 (23.9%)	58.0	
no	220 (76.1%)	39.5	
Congestive heart failure			.86
yes	19 (6.6%)	47.0	
no	270 (93.4%)	40.5	
Hypertension			.71
yes	166 (57.4%)	40.5	
no	123 (42.6%)	43.0	
Diabetes			.25
yes	74 (25.6%)	54.5	
no	215 (74.4%)	38.0	
Chronic obstructive airway disease			.99
yes	42 (14.5%)	39.5	
no	247 (85.5%)	43.0	
Psychiatric disorders			.09
yes	35 (12.1%)	74.0	
no	254 (87.9%)	38.5	

Table 2
The association between lagtime (between referral and diagnosis) and CRC stage at diagnosis in all study patients (n=289) and in a subset of patients with abnormal CRC screening tests. *p values from Wilcoxon test for duration variable, and from Chi square for the rest

	Lagtime (Median, Days)	Lag >Median (41 days)	Lag >60 days	Lag >90 days
All patients (n=289) (%)	41.0	145 (49.8%)	120 (41.5%)	87 (30.1%)
A (n =100) (34.6%)	62.0	63 (63.0%)	51 (51.0%)	39 (39.0%)
B (n = 83) (28.7%)	41.0	42 (50.6%)	34 (41.0%)	25 (30.1%)
C (n = 55) (19.0%)	31.0	24 (43.6%)	20 (36.4%)	12 (21.8%)
D (n = 51) (17.7%)	18.0	16 (31.4%)	15 (29.4%)	11 (21.6%)
<i>P value</i>	0.39	0.78	0.98	0.61
Patients with abnormal CRC screening (n=100)	60.0	55 (55.0%)	50 (50.0%)	40 (40.0%)
A (n=52)	60.0	31 (59.6%)	26 50.0(%)	22 (42.3%)
B (n=24)	62.0	12 (50.0%)	12 (50.0%)	10 (41.7%)
C (n=13)	12.0	6 (46.2%)	6 (46.2%)	3 (23.1%)
D (n=11)	80.0	6 (54.6%)	6 (54.6%)	5 (45.5%)
<i>P value</i>	0.39	0.78	0.98	0.61

Table 3
Risk of mortality among 289 patients diagnosed with CRC at MEDVAMC during January 1, 2000 to June 30, 2005. 83 have died during follow up that ended in August 1, 2007. Results of a multivariable Cox proportional hazard model

Variable	Level	Hazard ratio	95% CI	p-value
Lag period between referral and CRC diagnosis (unadjusted)	>= median lag (41 days)	0.61	0.39-0.96	.03
	< median lag	ref		
Lag period (adjusted*)	>= median lag	0.75	0.47-1.21	.24
	< median lag	ref		
Earliest treatment				<.0001
	endoscopic resection	0.08	0.03-0.20	<.0001
	radio or chemotherapy	0.34	0.16-0.74	.006
	surgical resection	0.08	0.04-0.17	<.0001
	none	ref		
Earliest initiator				.01
	abnormal lab or CT scan	0.69	0.40-1.21	.20
	family history of CRC	1.12	0.33-3.79	.86
	abnormal CRC screening	0.36	0.20-0.67	.001
	symptoms	ref		
Anatomic location				.005
	left colon	1.64	0.85-3.17	.14
	right colon	3.33	1.57-7.08	.002
	rectum	ref		
Duke stage				<.0001
	A	ref		
	B	1.41	0.55-3.63	0.48
	C	1.48	0.55-4.01	0.44
	D	5.69	2.26- 14.35	0.0002

* adjusted for the 4 variables listed below it in the table.

Table 4
Association between risk of mortality and the duration of lag period between referral and diagnosis of CRC in 289 patients (83 deaths) diagnosed during January 1, 2000 to June 30, 2005 at the MEDVAMC

	Adjustment	Hazard Ratio	95% CI	p-value
Lag between Referral and CRC Diagnosis*	None	0.84	0.73-0.97	.02
	Stage CRC at diagnosis	0.95	0.82-1.10	.49
	CRC Treatment	0.89	0.77-1.02	.10

* Modeled as log lag

Table 5
Potential determinants of lag period between CRC diagnosis and receipt of cancer directed therapy in 289 patients diagnosed with CRC during January 1, 2000 to June 30, 2005 at MEDVAMC

Variable	Level	n	Median Duration (days)	p-value
CRC treatment				<.0001
	Endoscopy	79	0	
	Surgery	140	16.5	
	Chemo/radiotherapy	46	41.0	
	None*	24	106.0	
Lag between referral and diagnosis				.55
	≥41 days	145	10.0	
	<41 days	144	14.0	
CRC stage at diagnosis				<.0001
	A	100	0	
	B	83	24	
	C	55	23	
	D	51	22	
Race				.88
	black	86	7.5	
	white	198	12.5	
	other	5	29.0	
Age				.11
	40-49	3	0	
	50-59	63	4.0	
	60-69	85	13.0	
	70-79	106	21.0	
	80+	32	7.0	
186 patients who received cancer directed treatment other than complete endoscopic resection (n=79); 24 did not receive cancer directed therapy.				
CRC location				.53
	Rectum	53	41.0	
	Left Colon	68	18.0	
	Right Colon	65	14.0	
CRC stage at diagnosis				0.32
	A	16	24.5	
	B	78	24.5	
	C	54	23	
	D	38	16	
Coronary artery disease				
	Present	144	20.0	.07

Variable	Level	n	Median Duration (days)	p-value
	Absent	42	35.0	
Congestive heart failure				
	Present	178	22.5	.51
	Absent	8	17.0	
Diabetes				
	Present	134	21.5	.25
	Absent	52	25.0	
Hypertension				
	Present	78	22.0	.61
	Absent	108	23.5	
Chronic obstructive airway disease				
	Present	160	22.0	.98
	Absent	26	24.0	
Psychiatric disorders				
	Present	164	23.0	.46
	Absent	22	19.5	