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Original Paper

Duration of Colorectal Cancer Symptoms and Survival: the Effect of Confounding Clinical and Pathological Variables

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The relationship between symptom duration and long-term survival following colorectal cancer is complex, and a number of factors may influence the length of time from onset of symptoms to cancer diagnosis. We prospectively studied 777 consecutive colorectal cancer patients to determine the association between symptom duration and survival independent of other clinical and pathological features. We used survival curves, the logrank test and Cox's proportional hazards model to assess possible changes in relative risk of death with increasing symptom duration, without making any a priori assumptions. We found that symptom duration shortened with advanced tumour stage ($P < 0.0006$) and was also shorter for patients presenting with bowel obstruction ($P < 0.0001$). Univariate survival analysis showed that long-term survival increased consistently with symptom duration ($P < 0.001$). However, when the effect of tumour stage and bowel obstruction were accounted for in a multivariate analysis, no decrease in the relative risk of death was seen as symptom duration increased. The addition of other variables to the proportional hazards model such as age, sex or tumour site did not further influence the risk function form of symptom duration. Our results suggest that early diagnosis of colorectal cancer should remain our goal when assessing patients with suggestive gastrointestinal symptoms. © **1997 Elsevier Science Ltd.**

Key words: colorectal neoplasms, symptom duration, prognosis, tumour staging, bowel obstruction, multivariate survival analysis

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INTRODUCTION

COLORECTAL CANCER is one of the most common cancers in the European Community, with over 150 000 cases per year [1]. The majority of large bowel cancers follow an orderly progression from normal mucosa to adenomatous polyp, early cancer and advanced disseminated disease [2] and long-term survival is inversely related to the extent of disease at surgery. This provides a rationale for asymptomatic screening, and both faecal occult blood testing and flexible sigmoidoscopy have been shown to reduce colorectal cancer-related mortality in average-risk populations [3, 4]. In addition to asymptomatic detection, a number of researchers have suggested that colorectal cancer mortality might also be decreased following early symptomatic detection through intensive case-finding, raising awareness of colorectal cancer symptoms in the population and the provision of open-access sigmoidoscopy [5–7]. However, many factors may influence the length of time from onset of symptoms to cancer diagnosis. These include the biological activity of the primary tumour, cultural influences, the fears and anxieties of individual patients and delays associated with health provision [8–11], all of which may interact in a complex manner [12].

Previous studies have attempted to assess the relationship between the duration of colorectal cancer symptoms, staging and survival, with conflicting results. Symptom duration was unrelated to colorectal cancer stage or survival in a number of studies [8, 9, 13–18], while others found that patients with a long symptom duration tended to have higher survival rates [19–22]. However, methodological problems have beset a large number of these studies, the majority being retrospective analyses of relatively few subjects and with inadequate follow-up times. In addition, univariate

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survival analyses failed to correct for potentially important or confounding clinical and pathological variables as proposed by Porta's group [23]. Finally, an important drawback of previous studies is that no attempt was made to determine the actual shape of the symptom duration risk function, that is, the change in relative risk of death with increasing symptom duration. We have prospectively studied a large consecutive series of colorectal cancer patients and have attempted to determine the association between symptom duration and survival independent of other clinical and pathological features, and without making a priori assumptions about the possible form of the symptom duration risk function.

PATIENTS AND METHODS

Seven hundred and seventy-seven consecutive symptomatic colorectal cancer patients (median age 68.4 years; range 26–92; males 417) admitted to St Vincent's Hospital, Dublin, between 1983 and 1992 were prospectively studied.

Patients were interviewed by a research registrar prior to diagnosis where possible, although many undergoing emergency surgery were interviewed postoperatively. Patients were questioned about the time of onset of symptoms which could be attributed to colorectal cancer and were specifically questioned about the occurrence of rectal bleeding, constipation, diarrhoea, tenesmus, weight loss, abdominal pain and the presence of a noticeable mass. Bowel obstruction was defined on clinical, radiographic and operative criteria [24]. Symptom duration was defined as the time between the onset of the first symptom and the date of surgery. Patients with bowel obstruction who had other, non-emergency, symptoms prior to obstruction were also questioned about the time of onset of obstructive symptoms. Twenty-one patients presenting as emergencies with either bowel perforation or a combination of perforation and obstruction were included with obstructed patients for the purpose of analysis.

All clinical, pathological and follow-up data were entered in a computerised colorectal cancer database as the information became available. Patients were followed up at three monthly intervals for the first year and yearly thereafter. Twenty-six patients (3.3%) were lost to follow-up over the 12 years of the study. The median follow-up of these patients was 4.8 years (range 1.2–10.2 years) prior to loss. For the purpose of survival analysis, patients lost to follow-up were censored at the time last known to be alive. Follow-up ended in January 1995 and median follow-up time was 5.4 years in patients alive at that time (including those lost to follow-up).

The left colon included the sigmoid colon, descending colon and splenic flexure. Tumours were staged according to the American Joint Committee on Cancer TNM staging system [25]. For the purposes of this study, tumours were divided into four stages. Stage I; T1-2, N0, M0: stage II; T3-4, M0, N0: stage III; T1-4, N1-3, M0: stage IV; any T, any N, M1 or Tx, Nx, M0-1.

Statistical methods

Associations between categorical variables were compared with the chi-square test. Non-parametric data were assessed with the Mann–Whitney U test, and Cuzick's test for trend was used to compare non-parametric data across multiple groups [26]. Kaplan–Meier survival curves were constructed with cancer-related death as the end point. Secondary analyses were performed with all cause mortality as the end-point to correct for any potential bias in the reporting of deaths. Differences in survival between groups were compared using the logrank test or the logrank test for trend as appropriate [27]. Multivariate survival analyses were per-

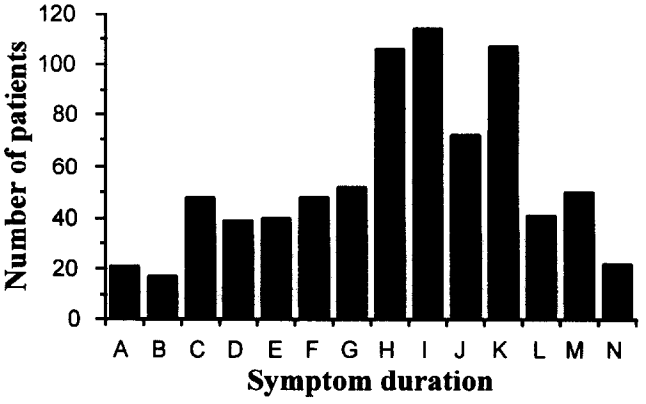

Figure 1. Histogram showing symptom duration. Group A, 0–0.1 months; B, >0.1–0.2 months; C, >0.2–0.3 months; D, >0.3–0.5 months; E, >0.5–0.9 months; F, 1 month; G, >1–1.75 months; H, >1.75–2 months; I, >2–3 months; >3–4 months; K, >4–6 months; L, >6–9 months; M, >9–12 months; N, >12 months.

Table 1. Relationship between clinico-pathological variables and symptom duration (months) in 777 colorectal cancer patients

	Number of cases	Sympton duration (median [I.Q. range])	*P* value
Year of diagnosis			
A (1983–1985)	155	2.0 (1.0–6.0)	
B (1985–1987)	156	2.0 (1.0–5.0)	
C (1987–1989)	155	3.0 (0.8–6.0)	0.54*
D (1989–1991)	156	2.0 (0.8–5.0)	
E (1991–1992)	155	3.0 (1.5–5.0)	
Patient age			
A (26–56 years)	155	3.0 (1.0–6.0)	
B (56–64 years)	156	2.5 (1.0–4.4)	
C (64–71 years)	155	3.0 (1.5–6.0)	0.07*
D (71–76 years)	156	2.0 (1.0–6.0)	
E (76–92 years)	155	2.0 (0.8–5.0)	
Patient sex			
Male	417	3.0 (1.0–6.0)	0.60†
Female	360	2.0 (1.0–5.0)	
Bowel obstruction			
Absent	616	3.0 (1.5–6.0)	<0.0001†
Present	161	0.8 (0.3–3.0)	
Tumour site			
Rectum	324	3.0 (1.5–6.0)	
Left colon	226	2.0 (0.8–4.0)	0.002*
Right colon	227	2.5 (0.8–5.0)	
Tumour stage			
Stage I	84	3.0 (1.3–6.0)	
Stage II	270	3.0 (1.3–6.0)	0.0006*
Stage III	199	3.0 (1.8–6.0)	
Stage IV	224	2.0 (0.8–4.0)	

I.Q. range, interquartile range.
*Cuzick's test for trend.
† Mann–Whitney U test.

Table 2. Relationship between tumour site and bowel obstruction in 777 colorectal cancer patients

	No obstruction ($n = 616$)	Obstruction ($n = 161$)	P value*
Tumour site			
Rectum ($n = 324$)	297 (92%)	27 (8%)	
Left colon ($n = 226$)	149 (66%)	77 (34%)	<0.0001
Right colon ($n = 227$)	170 (75%)	57 (25%)	

*Chi-square test (two degrees of freedom). P value for difference between left and right colon was 0.04.

formed with the Cox proportional hazards model using the Statistical Package for the Social Sciences (SPSS, Chicago, Illinois, U.S.A.). Model assumptions were verified by observing constant vertical differences between plots of the logarithm of the integrated hazard function for each variable [28]. P values are two-sided and P values less than 0.05 were considered statistically significant in all analyses.

The distribution of symptom duration was divided into quintiles in order to develop usable risk function forms of the effect of symptom duration on survival (group A, symptoms <1 month; group B, symptoms 1–2 months; group C, >2–3 months; group D, symptoms >3–6 months; group E, symptoms >6 months). The resulting groups contained different numbers of patients, but were as close to quintiles as it was possible to achieve. The risk of cancer-related death for patients in groups B, C, D and E was calculated relative to that of patients in group A (the reference group).

Risk function forms for symptom duration were calculated using the Cox proportional hazards model. Other factors such as patient age, patient sex, bowel obstruction, tumour site and tumour stage were introduced into the proportional hazards model sequentially and their effect on the symptom duration risk function form was noted.

RESULTS

Symptom duration and clinico-pathological variables

Figure 1 shows the distribution of symptom duration in 14 different groups. The median symptom duration for the patient population was 3 months (mean 3.88 months; range 1 day–2 years). Table 1 shows the relationship between symptom duration and clinico-pathological variables in all 777 patients. There was a trend towards longer symptom duration in younger than in older patients ($P = 0.07$), but

Table 3. Univariate survival analysis and multivariate Cox regression analysis of clinical and pathological features in 777 colorectal cancer patients

	Univariate analysis			Final regression model	
	Number of cases	% 5 year survival	P value	Relative risk (95% CI)	P value
Time of diagnosis (year)*					
A (1983–1985)	155	33.3			
B (1985–1987)	156	47.8			
C (1987–1989)	155	43.7	0.26‡		
D (1989–1991)	156	42.9			
E (1991–1992)	155	47.9†			
Patient age*					
A (26–56 years)	155	42.1			
B (56–64 years)	156	40.7			
C (64–71 years)	155	47.9	0.33‡		
D (71–76 years)	156	42.9			
E (76–92 years)	155	35.7			
Patient sex					
Male	417	39.9			
Female	360	44.5	0.32§		
Symptom duration*					
A (< 1 month)	165	30.7			
B (1–2 months)	206	37.2			
C (> 2–3 months)	114	43.5	<0.0001†		
D (> 3–6 months)	179	50.3			
E (> 6 months)	113	53.1			
Bowel obstruction					
Absent	616	47.1	<0.0001§	1	
Present	161	20.9		1.4 (1.2–1.8)	0.0008
Tumour site					
Rectum	324	43.6			
Left colon	226	36.1	0.19‡		
Right colon	227	45.5			
Tumour stage					
Stage I	84	83.1		1	
Stage II	270	64.2	<0.0001‡	2.4 (1.4–4.1)	0.002
Stage III	199	38.8		4.8 (2.9–8.3)	<0.0001
Stage IV	224	3.0		20.7 (12.1–35.4)	<0.0001

CI, confidence interval. *Entered as continuous variable into multivariate analysis. †Per cent survival at 4 years. ‡Logrank test for trend. §Logrank test.

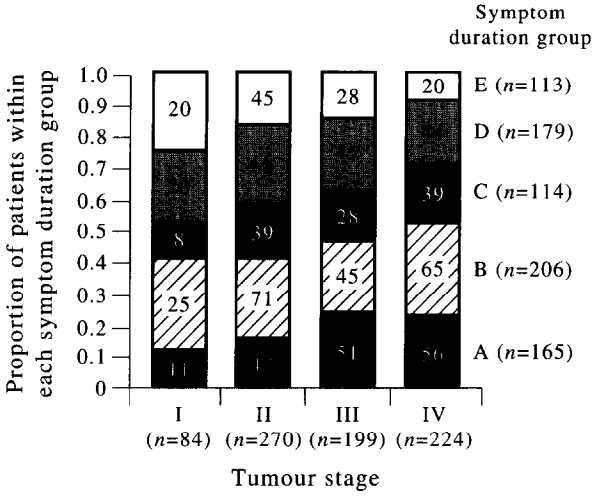

Figure 2. Proportion of patients within each tumour stage with symptoms <1 month (group A); 1–2 months (group B); >2–3 months (group C); >3–6 months (group D); and >6 months (group E). Figures within bars represent numbers of patients within each symptom duration group.

symptom duration was unrelated to year of diagnosis ($P = 0.54$) or patient sex ($P = 0.60$). Twenty-one per cent of cases presented with bowel obstruction, and these patients had a shorter symptom duration when compared to those without obstruction ($P < 0.0001$). Symptom duration was longer for patients with rectal cancer than those with colon cancer, and was shortest for those with tumours situated in the left colon. This finding may be related to the high incidence of obstruction tumours sited in the left colon when compared to the rectum (Table 2). Patients with stage IV disease had the shortest symptom duration (Table 1; $P = 0.0006$). Figure 2 shows that a relatively large proportion of patients with early staged disease had symptoms for longer than 6 months and that relatively few had symptoms for less than 1 month prior to diagnosis (chi square test for trend, $P = 0.0001$).

Univariate survival analysis

Five-year survival of the patient population was 42%, and the median survival time was 3.2 years. Table 3 and Figure 3 show the results of a univariate survival analysis of patients stratified by clinical and pathological features. Survival was unrelated to patient age, patient sex or tumour site. Tumour stage was the most powerful prognostic indicator studied and only 3% of patients with stage IV disease survived five years. Five-year survival was poor for those presenting with bowel obstruction compared to those without obstruction ($P < 0.0001$). The univariate survival analysis also showed that survival increased consistently with symptom duration (Table 3 and Figure 3; $P < 0.0001$). The five-year survival rate was 53% for patients with symptoms greater than six months compared with 31% for those with symptoms less than one month. Our secondary analysis closely paralleled our primary analysis except for older patients who had a higher all-cause mortality when compared with younger patients (data not shown).

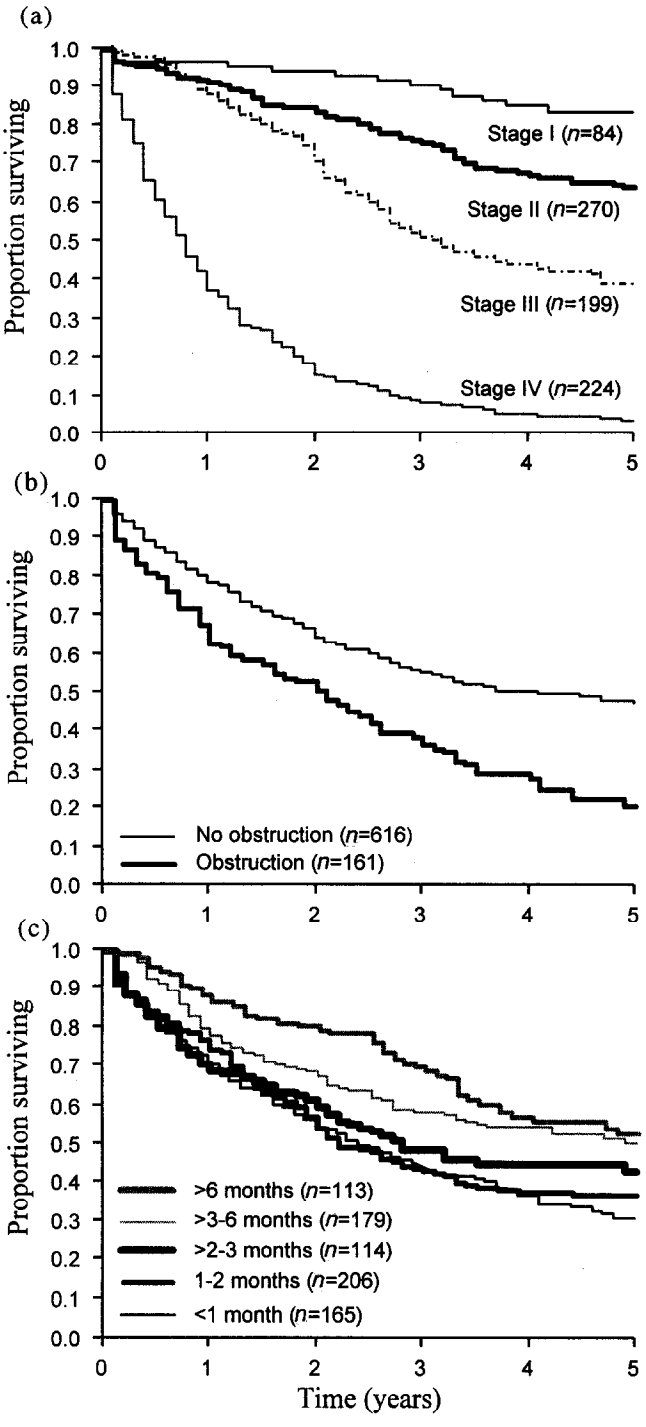

Figure 3. Five-year survival of 777 colorectal cancer patients stratified by (a) tumour stage, (b) presence of bowel obstruction at operation and (c) symptom duration.

Multivariate survival analysis

All clinical and pathological variables were entered into a Cox regression model to determine features independently related to cancer death, and the final model is shown in Table 3. Tumour stage and the presence of bowel obstruction were the only variables included in the final model, and both forward and backward regression produced the same result. In the final model, the risk of death for patients with bowel obstruction is relative to that of unobstructed

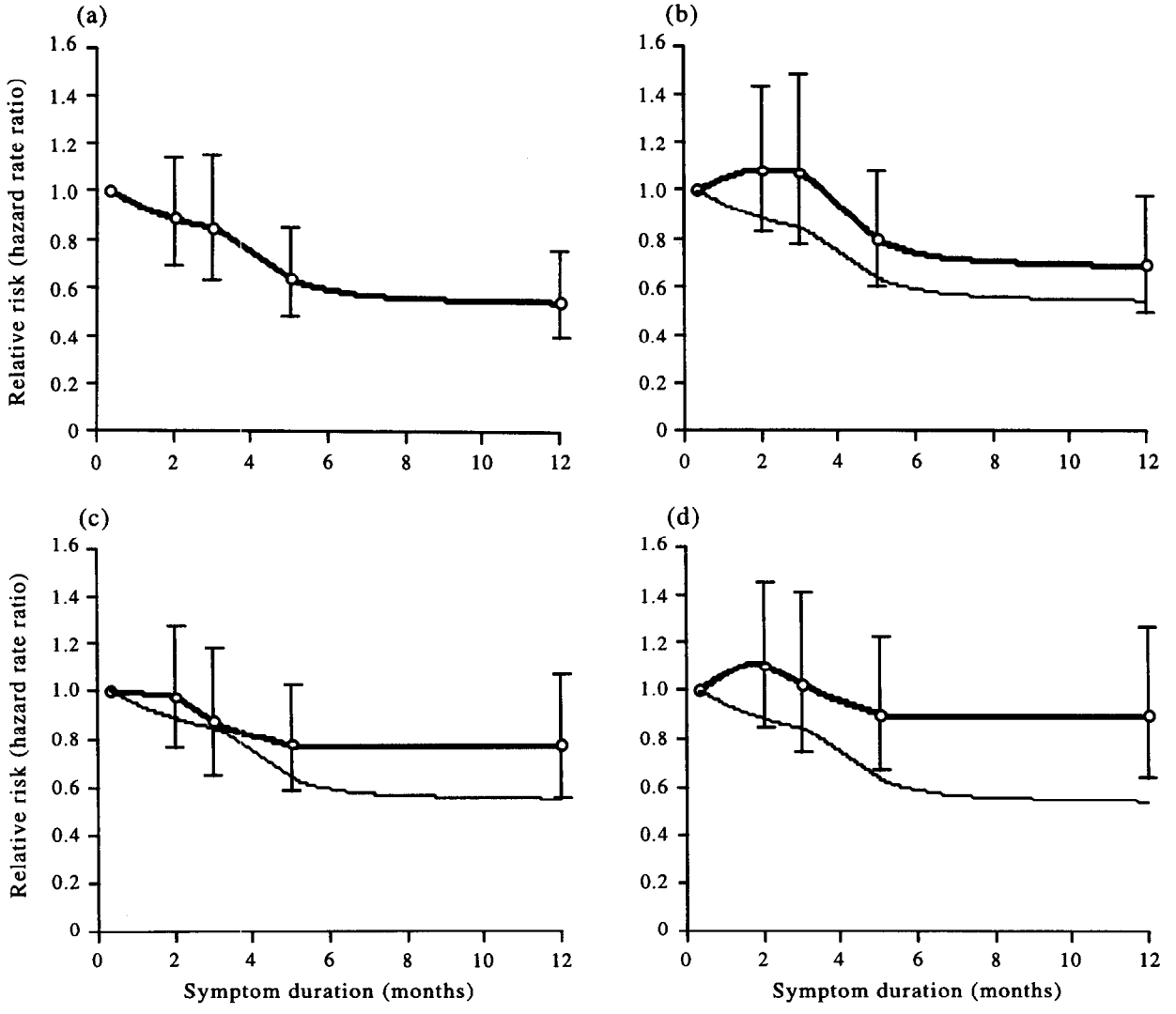

Figure 4. Risk function form of the effect of symptom duration on survival in 777 colorectal cancer patients. (a) Unadjusted risk function form. (b) Risk function form adjusted for bowel obstruction (fine line represents superimposed unadjusted risk function form). (c) Risk function form adjusted for tumour stage. (d) Risk function form adjusted for both bowel obstruction and tumour stage. Error bars represent 95% confidence intervals. Note that solid lines do not represent a continuum of risk, and that risk is only indicated at the 5 quintile points.

patients, while the risk of death for patients with stage II, III and IV disease is relative to that of patients with stage I disease. Although symptom duration was significantly related to outcome by univariate analysis, this variable was not included in the regression model because of its close association with both bowel obstruction and tumour stage.

Unadjusted and adjusted risk function forms for symptom duration

Figure 4 shows the unadjusted and adjusted risk function forms for symptom duration. Figure 4(a) shows that the relative risk (RR) of death fell consistently with increasing symptom duration and was significantly lower for patients within group D (RR 0.64, 95% CI 0.49–0.85, $P = 0.002$) and group E (RR 0.55, 95% CI 0.40–0.76, $P = 0.0003$) compared to group A. When symptom duration was corrected for the confounding effect of bowel obstruction (Figure 4(b)), the relative risk of death was found to rise initially before again falling as symptom duration increased further. In this model the relative risk was significantly lower for patients within group E (RR 0.69, 95% CI 0.40–0.97, $P = 0.03$) compared to group A. When symptom duration was adjusted for tumour stage (Figure 4(c)), the relative risk decreased only slightly as symptom duration increased, and no significant differences in relative risk were seen between quintiles. Finally, Figure 4(d) shows the risk function form when symptom duration was adjusted both for bowel obstruction and tumour stage. In this model, the relative risk of death for patients in all five groups was close to 1. Further addition of other variables to the model including age, sex and tumour site did not alter the symptom duration risk function form to any significant extent (data not shown). Figure 5 shows the risk function form for symptom duration when stratified by tumour stage. The risk of death was highest for patients with stage I/II tumours and for stage IV tumour who had a short duration of symptoms. Patients with stage III disease with symptoms for between 1 and 2 months had an especially high relative risk of death.

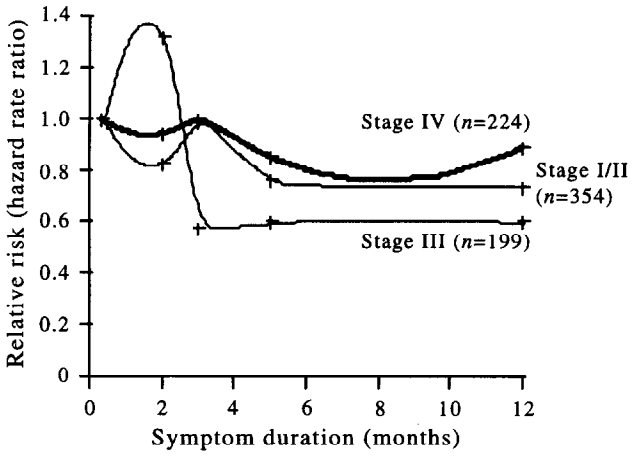

Figure 5. Risk function form of the effect of symptom duration on survival in 777 colorectal cancer patients stratified by tumour stage.

Bowel obstruction and other symptoms prior to obstruction

In the subset of patients with bowel obstruction at diagnosis, obstruction was noted as the only presenting feature in 94 (58%) of the 161 cases (Table 4). The remaining 67 patients (42%) had experienced other non-obstructive colorectal symptoms for a median 2.9 months prior to the onset of obstruction.

DISCUSSION

A number of previous studies have examined the relationship between symptom duration and colorectal cancer survival with conflicting results [8, 9, 13–22]. Porta's group, in a more recent study of seven different cancer types, found that the relationship between symptom duration and survival could be influenced by other variables and that the relative risk of death did not necessarily change in a linear manner as symptom duration increased [23]. The results of our study confirm the complex relationship between symptom duration and colorectal cancer outcome. Although the duration of symptoms correlated inversely with survival in our simple univariate analysis, this resulted from a close interaction with both the mode of presentation and tumour stage. Thus, symptom duration had no effect on colorectal cancer outcome when we corrected for these more powerful clinical and pathological variables in a multivariate analysis.

In common with most other studies of colorectal cancer, we found that both tumour stage and the presence of bowel obstruction at diagnosis were important and independent variables affecting outcome in our patient population [29–32]. In addition, both of these features were significantly related to symptom duration. It is hardly surprising that patients with bowel obstruction or perforation tended to present as emergencies soon after the onset of these intrusive symptoms, but is is less clear why symptom duration was inversely related to tumour stage. A possible explanation is that a proportion of patients with pathologically advanced disease at diagnosis had fast-growing biologically aggressive tumours which caused a relatively rapid onset of debilitating symptoms [22]. However, one would need to assess the relationship between tumour stage and the increase in severity of individual symptoms over time to determine if this was indeed the case.

The main finding from our study was that there was little association between symptom duration and patient survival when symptom duration was corrected for other important prognostic variables. However, this does not necessarily imply that a reduction in diagnostic delay will have little or no effect on improving colorectal cancer outcome, as suggested by some authors [8, 9, 33]. Firstly, although we took care to measure symptom duration accurately, we cannot rule out the possibility that recall biases in ill patients or interactions between symptom duration and other unmeasured psychological or social factors might have affected our results [23, 34]. Secondly, the lack of correlation between symptom duration and survival in a large population does not exclude the possibility that individual tumours progress during the symptomatic period and that such cases would benefit from early symptomatic diagnosis [14, 19, 34]. Finally, we found that over 40% of patients presenting with bowel obstruction had experienced other symptoms prior to the onset of obstruction. Early presentation and investigation of these patients would certainly have led to fewer cases of obstruction, known to be an independent risk factor for both postoperative and long-term mortality [30–32]. Taking these factors into account, it seems sensible to conclude that early diagnosis of colorectal cancer should remain our goal when assessing patients with suggestive gastrointestinal symptoms.

Table 4. Duration of bowel obstruction (months; median [interquartile range]) and duration of symptoms prior to bowel obstruction in 161 colorectal cancer patients

	Obstruction as first symptom (n = 94)	Other symptoms as first symptom (n = 67)
Duration of bowel obstruction	0.3 (0.2–0.5)	0.3 (0.2–0.5)
Symptom duration prior to onset of bowel obstruction	–	2.9 (1.8–4.5)
Total symptom duration	0.3 (0.2–0.5)	3.0 (2.0–5.0)

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