



Colorectal Cancer Survival is not Affected by Delay in Diagnosis

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Abstract

Introduction: We previously published that patients were significantly less likely to have Australian clinicopathological stage (ACPS) 'A' colorectal cancer (CRC) tumours if there had been delayed diagnosis or if they were male. The aim of this study was to evaluate in the same group of patients the effects of delayed diagnosis, gender, age, tumour site and stage on long term survival.

Methods: All 100 patients from the 1995 study were followed up until death or between October 2000 and December 2000. Cancer specific survival (CSS) and overall survival (OS) curves were calculated by Kaplan-Meier method and compared by the log-rank test. Multivariate analysis was performed by Cox proportional hazards model.

Results: The entire cohort's 5-year CSS was 51% and OS was 44%. Survival was significantly better for stage A tumours (CSS and OS $p < 0.001$) and for right sided CRC tumours (CSS $p = 0.026$, OS $p = 0.037$). Delayed diagnosis, gender and age were not significantly associated with survival (CSS or OS). Tumour site and stage remained significant independent prognostic indicators of survival on multivariate analysis.

Conclusion: Delay in diagnosis of symptomatic CRC does not have an effect on long-term cancer specific or overall survival. This does not detract from the importance of early diagnosis in clinical practice but reinforces the role of tumour site and stage in survival of CRC.

Keywords: Colorectal cancer; Delayed diagnosis; Survival

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Introduction

Colorectal cancer (CRC) is the most common cancer reported to the Australian cancer registries and is the second leading cause of cancer death after lung cancer in 2001 [1]. The lifetime risk of colorectal cancer before the age of 75 is about one in 17 for males and one in 26 for females with incidence increasing progressively with age [1].

Most will agree that the earlier the stage at diagnosis the higher the chance of survival from CRC. Hospital registries from teaching hospitals in South Australia show that five year CRC survival rates varies with the Australian Clinicopathological Stage (ACPS) [2] and is similar to the results published elsewhere [3,4]. There is evidence from population based randomised controlled trials that faecal occult blood screening tests reduce overall mortality from CRC [5-7]. It is logical to assume that improved survival and reduction in mortality from CRC could be achieved by earlier diagnosis given that only 15% of CRC in South Australia were diagnosed at ACPS stage A (confined to the muscularis propria) [2]. Delay in seeking care has been proposed as a major reason for significantly lower survival from CRC in lower socio-economic groups [8].

We previously demonstrated that patients were less likely to have a stage A CRC if there was a delay in diagnosis or if they were males [9]. The aim of this study was to evaluate the effects of delayed diagnosis, gender, age, tumour site and stage on long term survival in the same group of patients from the 1995 study.

Methods

All 100 patients from the original study who were symptomatic patients with invasive adenocarcinoma that underwent excision of their tumours were followed up between October 2000 and December 2000 [9]. These patients had their resections for CRC at the Royal Adelaide Hospital colorectal unit between December 1994 and November 1995. Data were collected by the clinical

Table 1: Univariate association between independent variables and colorectal cancer-specific survival (CSS) and overall survival (OS).

Variable	n (and %)	Five-year mean CSS, % (95% CI)	Univariate p-value	Five-year mean OS, % (95% CI)	Univariate p-value
Gender					
Male	52	46.79 (39.22-54.37)	0.193	39.50 (32.43-46.57)	0.068
Female	48	55.72 (48.28-63.16)		47.43 (39.18, 55.69)	
Age (years)					
< 70	43	50.61 (42.11-59.11)	0.774	47.88 (39.44-56.32)	0.16
≥ 70	57	52.50 (45.13-59.87)		40.25 (33.03-47.46)	
Delay in diagnosis of colorectal cancer					
Delay	34	51.83 (41.96-61.70)	0.783	43.97 (34.33-53.62)	0.887
No delay	66	51.74 (45.10-58.38)		43.45 (36.68-50.21)	
Site of colorectal tumour					
Right	30	62.72 (55.12-70.32)	0.026	55.23 (46.47-64.00)	0.037
Left	29	44.80 (33.68-55.92)		36.89 (26.46-47.32)	
Rectum	41	47.80 (38.94-56.67)		39.49 (30.91-48.07)	
Tumour ACP Stage					
A	16	70.00 (66.28-73.72)	<0.001	59.06 (47.07-71.06)	<0.001
B	34	62.88 (56.88-68.88)		49.54 (41.94-57.14)	
C	35	50.50 (41.12-59.88)		44.98 (35.55-54.42)	
D	15	9.42 (5.25-13.59)		8.80 (4.86-12.74)	

ACP: Australian Clinicopathological; CI: Confidence Interval

research manager of the colorectal unit or by one of the authors (CJY) from the clinical records, General Practitioners notes or from the death registry. Patients or their relatives were interviewed in some cases. The variables recorded for analysis include date of death or last follow up, months to death or last follow up and cause of death, along with the others mentioned in our original study [9].

From the original study, delay was defined to have occurred if more than a three month period had lapsed from the time when initial symptoms were clearly established and the time of operation [9]. This occurred in 34 of 100 patients (34%) with the remaining 66 patients had no delay. In keeping with the original study, we further analysed tumour stage comparing patients with Stage A tumours with a combined Stages B, C and D group, and further analysed tumour site comparing right sided tumours (caecum to transverse colon) with a combined left sided (splenic flexure to sigmoid) and rectum group.

Survival curves were generated by the Kaplan-Meier method, and the log rank test was utilised to compare survival curves. Multivariate analysis was performed by the Cox proportional hazard regression model. A value of $p < 0.05$ was considered statistically significant. 95% confidence interval (95%CI) was calculated for variables including gender, age, and delay in diagnosis, tumour site and stage. All statistical analyses were performed using IBM-SPSS version 24 (IBM Corp).

Results

All patients from the original study were followed up until death or between October 2000 and December 2000. This includes 15 patients who had an emergency bowel resection (5 in the delay group and 10 in the no-delay group). Twenty-one patients had a stoma as part of their operation. The entire 100 patient cohort's 5-year CSS was 51% and OS was 44%.

Univariate analyses with the 5-year CSS and OS rates and mean survival times are shown in Table 1. Survival was significantly better for stage A tumours (CSS and OS $p < 0.001$) and for right sided CRC tumours (CSS $p = 0.026$, OS $p = 0.037$). Gender, age and delayed diagnosis status were not significantly associated with survival (CSS or OS). Survival curves, using the Kaplan-Meier method, are presented in figures 1-4 for the significant variables of tumour site and stage.

In the Cox proportional hazards model (Table 2), variables

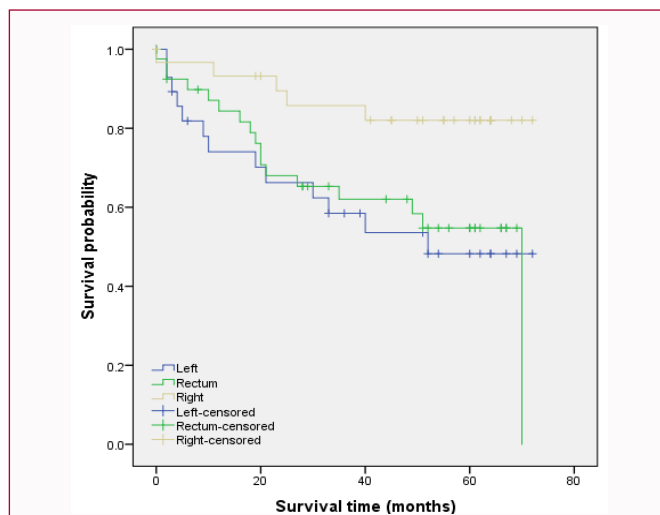


Figure 1: Kaplan-Meier cancer specific survival curve – Colorectal tumour site.

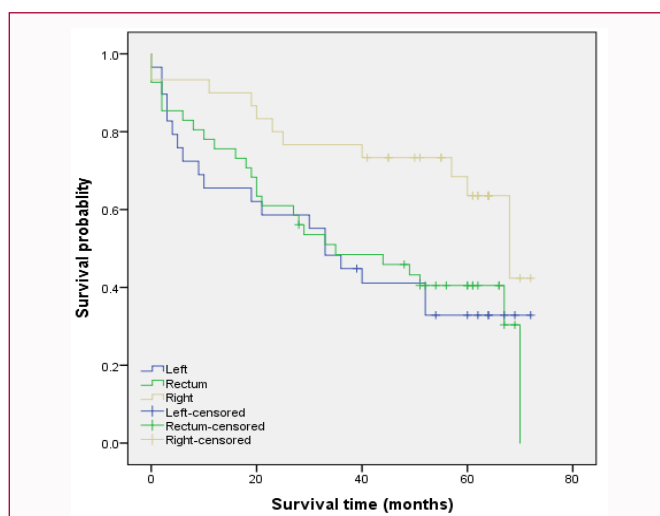
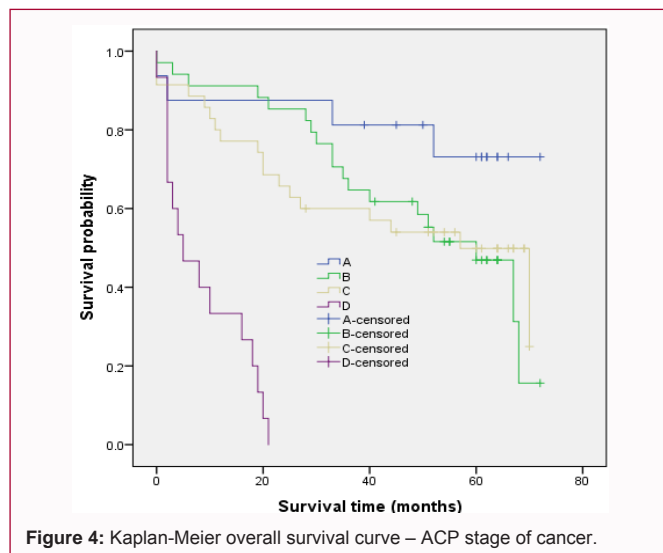
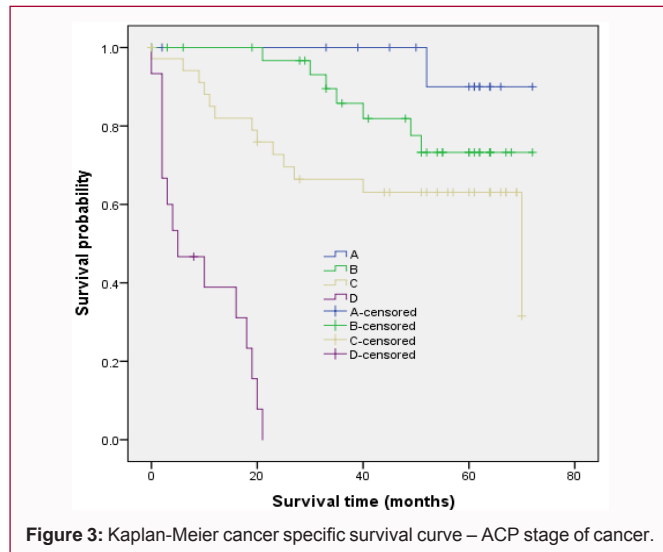


Figure 2: Kaplan-Meier overall survival curve – Colorectal tumour site.

including age and delay status were rejected from the model. Tumour site and stage remained significant independent prognostic indicators of survival (CSS and OS) on multivariate analysis.



Discussion

Our original study looked at the prevalence and reasons for delay in diagnosis of symptomatic CRC and the effects of delay, gender, and age and tumour site on the stage of the disease at presentation and demonstrated that only the gender of the patient had a significant effect on tumour stage [9]. The present study evaluates the effects of delay in diagnosis, gender, age and tumour site and stage on 5 year survival in the same group of patients.

We did not find any difference in the 5 year survival rates between patients who had diagnosis and surgery of symptomatic CRC within 3 months of onset of symptoms and patients who had a delay in diagnosis of more than 3 months. Fifteen of the 34 patients in the delay group had a delay of more than 9 months. The relationship between duration of symptoms and survival in CRC has been previously

reported. Many authors agree with our observation that symptom duration is not related to survival [10-14], whereas others believe that prolonged duration of symptoms is associated with advanced stage of tumour and poor survival [15,16]. Given that there is good evidence that screening reduces mortality from asymptomatic CRC [5-7] it may be possible that prognosis of CRC is already determined when symptoms are present as suggested by this study. Rupasarra and colleagues even reported improved survival for patients with delayed diagnosis of symptomatic CRC [17], while the review of Ramos et al. [18] reported 26 studies with no association between delay and survival, four had better prognosis, and two had poorer prognosis.

It is well recognised that CRC survival is directly related to the stage of the disease [2-4] and hence it was not surprising that we found a significant 5 year survival benefit in ACP stage A patients compared with stage B, C and D. The entire cohorts 5-year CSS was 51% and OS was 44%, and twenty of the 55 patients who died during the course of the study died of inter current disease.

In the present study tumours proximal to splenic flexure had a significantly better prognosis than distal tumours. The effect of tumour site on survival remains unclear. Right colon cancer was found to have favourable prognosis by Halvorsen et al. [19] and Wolmark et al. [20] whereas others noted better prognosis for sigmoid colon tumours [21]. Kune et al. [22] confirmed better survival in right colon cancer in multifactorial analysis. Gervaz et al. [23] in their recent paper conclude that tumours arising from the proximal colon have a better prognosis due to high percentage of MSI positive lesions. Diez et al. [24] demonstrated that p53 over expression, which was associated with lower disease free survival was more frequent in distal than in proximal tumours.

The relationship between gender and outcome following surgery for CRC remains controversial. We did not observe any significant difference in survival between men and women even though there was a trend towards better overall survival in women. Coleman et al. [25] reported a 1-2 % survival advantage in women with rectal cancer but found no difference in survival at 5 years between genders in colonic cancer. However Ratto et al. [26] in his review of 18 studies found only four where gender appeared to have a significant effect on outcome. Wichmann et al. [27] noticed significantly longer disease free survival and overall survival in women following curative resection of rectal cancer but found no difference in colon cancer. McArdle et al. [28] reported a significant improvement in overall 5 year survival in women in both colon and rectal cancer but interestingly the cancer specific 5 year survival advantage was greater in women who had colonic resection than rectal tumours. We did not analyse the survival of colon and rectal cancer separately in men and women due to the relative small number of patients involved in the study. The small sample size is a weakness overall of this study. Strength is the 100% follow-up of all the patients involved.

We elected to compare the survival of patients under the age of 70 years with older patients as the mean age of patients in our group was 70.4 and we had only 8 patients under the age of 50 years. We did

Table 2: Multivariate analysis of prognostic factors influencing colorectal cancer-specific survival (CSS) and overall survival (OS).

Risk factors	CSS HR (95% CI)	p-value	OS HR (95% CI)	p-value
Gender	0.81 (0.41-1.63)	0.562	0.74 (0.43-1.29)	0.285
Site of colorectal tumour (Right vs. Left and Rectum)	3.22 (1.24-8.37)	0.016	2.19 (1.13-4.26)	0.021
Stage (A vs. B,C and D)	7.51 (1.02-55.27)	0.048	2.83 (1.01-7.90)	0.048

HR: Hazard Ratio; CI: Confidence Interval

not observe any significant difference in 5 year survival between the 2 groups (43 patients < 70 years; 57 patients ≥ 70 years). Some argue that young age is associated with poor prognosis [29,30] yet others believe that 5 year survival is better in younger patients [31,32]. Five of our 8 patients under the age of 50 years had advanced disease (ACPS stage C or D).

Conclusion

Delay in diagnosis of more than 3 months from onset of clearly established symptoms does not have an effect on long term cancer specific survival or overall survival for patients undergoing resection for symptomatic CRC. Site of the tumour and stage of the disease at presentation are the most significant independent prognostic factors.

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