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Prognostic Factors in Patients With Colorectal Cancer at Hospital Universiti Sains Malaysia

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OBJECTIVE: To determine the 5-year survival rate and prognostic factors for survival in patients with colorectal cancer treated at the Surgical Unit, Hospital Universiti Sains Malaysia (HUSM), Kelantan, Malaysia.
METHODS: We retrospectively reviewed the records of 115 patients treated in HUSM from 1996 to 2005. Data of variables considered as prognostic factors were obtained from the records. Simple and multiple Cox proportional hazard regression using the stepwise method were used to model the prognostic factors for survival.
RESULTS: We found that the significant prognostic factors were liver metastases [adjusted hazard ratio (HR): 3.75; 95% confidence interval (CI): 1.95–7.22], Dukes C stage (adjusted HR: 4.65; 95% CI: 2.37–9.11), Dukes D stage (adjusted HR: 6.71; 95% CI: 2.92–15.48) and non-surgical treatment (adjusted HR: 3.75; 95% CI: 1.26–11.21).
CONCLUSION: Colorectal patients treated at HUSM with Dukes C staging, presence of liver metastases and received treatment with both chemotherapy and radiotherapy are at the greatest risk of death from colorectal cancer. [*Asian J Surg* 2010;33(3):127–33]

Key Words: colorectal cancer, Cox proportional hazards model, survival analysis

Introduction

Colorectal cancer is the third most common cancer worldwide after lung and breast cancer; it accounts for an estimated more than one million new cancer cases and over 590,000 cancer deaths per year, which is almost 10% of all cancer deaths.[1,2] Asian countries, including China, Japan, South Korea and Singapore, have experienced a 2–4-fold increase in the incidence of colorectal cancer during the past few decades.[3] It was the most common cancer in Singapore, while in Malaysia, it was the third most common cancer among males and females with prevalences of 7.6% and 6.0%, respectively. On the other hand, rectal cancer was the fifth most common cancer with prevalences of 6.6% in males and 4.1% in females.[4,5]

Multiple prognostic factors that affect the survival of patients with colorectal cancer have been identified, e.g. Dukes stage, number of lymph nodes involved, lymph node metastases, preoperative carcinoembryonic antigen (CEA) level and tumour location.[6–9] The best estimate of prognosis in colorectal cancer is related to the anatomic extent of disease determined by the pathological examination of the resected specimen.[10] However, the accurate determination of prognostic factors for colorectal cancer

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remains a problem and further studies are needed to determine the role of clinical and pathological factors in colorectal cancer especially for local data in Malaysia.[6]

Thus we performed a study to determine the pattern of survival and prognostic factors for patients with colorectal cancer treated at the Surgical Unit, Hospital Universiti Sains Malaysia (HUSM), a large tertiary hospital in Malaysia. To the best of our knowledge, there has been no published localised study on prognostic factors for colorectal cancer, and identification of prognostic factors can help in the management of patients and in planning better intervention and prevention programs for such patients, particularly in Malaysia.

Patients and methods

This was a retrospective record review study, in which we obtained, from the HUSM record office, the medical records of patients diagnosed with colorectal cancer and treated in HUSM from 1996 until the end of 2005. The reference population for this study comprised all patients with colorectal cancer admitted to HUSM, while the source population was all patients diagnosed with colorectal cancer and treated in HUSM over 10 years (1996–2005).

The inclusion criteria were patients with confirmed diagnosis of colorectal cancer based on histopathological findings as defined by the International Classification of Disease Clinical Modification 9th edition ICD-9-CM code (153.0–154.1) for cases pre-2000 and ICD-10 code (C.18–C.20) for cases post-2000, and patients who had a history of being treated at least once at HUSM.[11] We excluded medical records with more than 30% incomplete information.

We calculated the sample size using the Power and Sample Size Calculation software program.[12] The level of significance, α and the power, $1 - \beta$, of the study were set at 0.05 (two-sided) and 0.80, respectively. The median survival time for patients who were on usual treatment and the ratio of control to experimental patients were obtained from the literature. The detectable hazard ratio was decided by the researcher and the senior surgeons who were managing the colorectal cancer patients in HUSM. The accrual patient recruitment time was 120 months. Ten percent of the final figure was added for the anticipation of some missing values and nonresponse cases, which made the final sample size for this study 140 patients.

The variables of interest were sociodemographic data such as age, race, sex, type of occupation and smoking status. The age of the patients was defined as age in years at the final diagnosis. This was performed by calculating the difference between the year of final diagnosis and the year the patient was born. The date of the final diagnosis was obtained from the histopathological examination report. The patients' race was categorized either as Malay or non-Malay, because patients in this part of Malaysia were mainly from the Malay ethnic group. Smokers were defined as patients who were smokers prior to the study recruitment phase irrespective of the amount of cigarettes smoked. Ex-smokers were those who had history of smoking but had already ceased smoking before they were diagnosed with colorectal cancer. Nonsmokers were those who had never smoked in their lifetime.

The clinical characteristics of interest were tumour site, stage at diagnosis, presence of metastases, per rectal bleeding, and CEA level. The tumour site was categorized according to the tumour location identified at the time of diagnosis. They were categorized into colon, rectum and rectosigmoid. Cancer of the colon was defined as a tumour in the ascending colon, descending colon, transverse colon, hepatic flexure, splenic flexure or transverse colon.

We used Dukes staging to classify the various stages of the colorectal cancer. As there was no patient in the Dukes A group in our study, the staging was thus classified into three categories only; Dukes B, Dukes C and Dukes D. The presence of metastases was categorized irrespective of when metastases had occurred. Only liver metastases had been chosen for study as the prognostic factor since it is the most common site of metastases in colorectal cancer.[13] Per rectal bleeding was determined according to the initial symptoms reported in the medical records regardless of its duration since it was rarely available in the patients' medical record. We used the preoperative assessment of CEA level where the CEA level was divided into ≤ 5 ng/mL and > 5 ng/mL and a CEA value of > 5 ng/mL was considered abnormal.[8] For comorbidities, we categorized them into three categories: without comorbidity, single comorbidity and two or more comorbidities. There were four treatment modalities: surgery, surgery with chemotherapy or radiotherapy, surgery followed by chemotherapy and radiotherapy, and chemotherapy and/or radiotherapy (nonsurgical treatment) alone.

The patients' survival status was classified into three categories: dead, alive or loss to follow-up. If the patient died, the date and cause of death were recorded. The cause

of death was categorized into death from colorectal cancer or death from other causes. The exact date and cause of death were obtained from the medical records. If the survival status was not available in the medical record, we acquired it by contacting the patients themselves or their relatives if the patients were not contactable. This was possible because the medical records contained the phone numbers and the addresses of the patients and their relatives.

Ethical clearance was obtained from the Research and Ethics Committee of HUSM (Reference number: USMKK/PPSP/JEPem, USM [194.4(3.3)]), Malaysia.

We used Stata/SE version 9.2 (StataCorp. College Station, TX, USA) for data entry and data analysis. The simple Cox regression analysis was conducted for all independent variables or predictors to screen the variables at the univariate level. The predictors were considered important if the *p* value was lower than 0.25.[14] The multiple Cox proportional hazard regression model was applied to model the prognostic factors. We used the full stepwise selection method for variable selection, and the *p* value of lower than 0.05 was chosen for variable entry, while the *p* value of greater than 0.1 was used for variable removal.

We tested two-way interaction terms between the variables in the preliminary main analysis, checked the presence of serious multicollinearity, examined the proportional hazards assumption and measured the goodness of fit and the diagnostic statistics for model adequacy. For all the predictor categorical variables, the assumption of proportionality was analyzed by inspection of the log cumulative hazard curve plotted against log time, also known as the log minus log plot. Additionally, we inspected the scaled Schoenfeld partial residual plot and evaluated the proportionality significance using the scaled Schoenfeld for each predictor variable and the Schoenfeld for global test. Martingale residuals were checked to determine the functional form of covariates to be included in the model and to assess the model's lack of fit. Cox Snell residuals were checked for overall model fitness. Deviance residual was assessed to examine the model accuracy and identifying outliers. The cut-off point for residual plot deviance was ± 4. The df-beta residual plot was examined to identify influential observations. The final model was presented with the adjusted hazard ratio (HR) with 95% confidence interval (CI) and its corresponding *p* value. The level of significance was set at 0.05 in two-tailed fashion.

Results

Data from 115 patients with colorectal cancer treated at the Surgical Unit, HUSM, were analyzed, and the results showed that the mean age of the colorectal patients was 55.7 years, 62.6% ($n = 72$) were male and 76.5% ($n = 88$) were from the Malay ethnic group. The 5-year survival rates along with their 95% CI, according to the sociodemographic and clinical profiles, are shown in Table 1. This shows that those patients who were older than 70 years, who were male, who had cancer of the colon classified as Duke B and who had two or more comorbidities have the highest survival rate.

In Table 2, we show the result from the simple Cox regression analysis. The predictor variables examined were age, sex, race, working status, smoking status, per rectal bleeding, liver metastasis, site of tumour, Dukes staging, preoperative CEA level and treatment modalities. The significant (*p* values less than 0.05) crude or unadjusted

Table 1. Five-year survival rate from Kaplan-Meier estimates ($n = 115$)

Variables	Survival rate (%)	95% Confidence interval	
		Lower limit	Upper limit
Age group (yr)			
16.0–49.9	30.3	15.8	46.1
50.0–69.9	31.4	18.1	45.5
≥ 70.0	53.3	26.3	74.8
Sex			
Male	38.4	22.5	54.1
Female	32.3	20.6	44.5
Race			
Malay	28.4	18.3	39.4
Non-Malay	52.9	29.7	71.5
Site of tumour			
Colon	43.9	29.1	57.7
Rectum	22.8	8.7	40.9
Rectosigmoid	29.3	11.1	50.5
Dukes staging*			
Duke B	68.4	50.3	81.1
Duke C	12.1	2.9	14.6
Comorbidities			
None	27.4	16.4	39.5
Single	37.4	12.1	63.3
Two or more	48.3	26.6	67.1

*Duke D cannot be determined because of the small sample size.

Table 2. Prognostic factors in simple Cox regression analysis*

Variables	Mean (SD) or *n* (%)	Crude HR (95% CI)	LR	*p*†
Age (yr)	55.7 (14.4)	0.98 (0.97–0.99)	4.04	0.044
Age group				
16–49	40 (34.8)	1.00	–	–
50–69	60 (52.2)	0.82 (0.50–1.35)	–0.77	0.440‡
≥ 70	15 (13.0)	0.63 (0.28–1.38)	–1.16	0.245‡
Sex				
Female	43 (37.4)	1.00	–	–
Male	72 (62.6)	1.08 (0.66–1.76)	0.10	0.75
Race				
Non-Malay	27 (23.5)	1.00	–	–
Malay	88 (76.5)	2.26 (1.19–4.30)	7.38	0.006
Per rectal bleeding				
No	58 (50.4)	1.00	–	–
Yes	57 (49.6)	1.28 (0.81–2.05)	1.10	0.294
Dukes staging				
B	50 (43.5)	1.00	–	–
C	38 (33.0)	5.19 (2.76–9.79)	5.10§	< 0.001‡
D	27 (23.5)	15.30 (7.57–30.9)	7.60§	< 0.001‡
Liver metastasis status				
No	70 (60.9)	1.00	–	–
Yes	45 (39.1)	5.74 (3.46–9.51)	46.1	< 0.001
Site of tumour				
Colon	48 (41.7)	1.00	–	–
Rectum	41 (35.7)	1.60 (0.93–2.75)	1.72§	0.086‡
Rectosigmoid	26 (22.6)	1.49 (0.80–2.79)	1.25§	0.211‡
Preoperative CEA level (ng/mL)				
≤ 5	45 (39.1)	1.00	–	–
> 5	70 (60.9)	3.39 (1.96–5.89)	22.3	< 0.001
Comorbidities				
None	68 (59.1)	1.00	–	–
Single	22 (19.1)	0.67	–1.25§	0.210‡
Two or more	25 (21.7)	0.54	–1.90§	0.057‡
Treatment modalities				
Surgery + chemotherapy + radiotherapy	20 (17.4)	1.00		
Surgery + chemotherapy or radiotherapy	59 (51.3)	0.97 (0.50–1.90)	–0.08§	0.938‡
Surgery alone	31 (27.0)	2.23 (1.10–4.51)	2.24§	0.025‡
Chemotherapy and/or radiotherapy	5 (4.3)	5.60 (1.92–16.31)	3.16§	0.002‡

*The fourth column shows the values of the Likelihood ratio (LR) test statistic unless mentioned specifically as Z value. The last column contains the corresponding *p* value of the LR test statistic or Wald test statistic; †*p* for LR statistic; ‡*p* for Wald statistic; §Z value for Wald statistic. HR = hazard ratio; CI = confidence interval; CEA = carcinoembryonic antigen.

prognostic variables were age, race, Dukes staging, liver metastases, preoperative CEA level and treatment modalities. The potential predictor variables in the simple Cox regression were those with *p* values of less than 0.25 and/or possessed clinical or biological importance. They were further analyzed in the multiple Cox regression analysis.

We used multiple Cox regression, also known as the proportional hazards model, to model the important

Table 3. Final model of prognostic factors of 115 patients with colorectal cancer using the multiple Cox proportional hazards regression model

Variables	Adjusted HR (95% CI)	*p**
Liver metastases		
No	1.00	–
Yes	3.75 (1.95–7.22)	< 0.001
Dukes staging		
B	1.00	–
C	4.65 (2.37–9.11)	< 0.001
D	6.71 (2.92–15.48)	< 0.001
Treatment modalities		
Surgery + chemotherapy + radiotherapy	1.00	0.212
Surgery + chemotherapy or surgery + radiotherapy	0.64 (0.32–1.28)	0.113
Surgery alone	1.81 (0.87–3.77)	0.018
Chemotherapy + radiotherapy	3.75 (1.26–11.21)	

**p* value for Wald statistics. HR = hazard ratio; CI = confidence interval.

predictors for survival in the patients. The significant prognostic factors from the final model of multiple Cox regression analysis were liver metastasis status, Dukes staging and treatment modalities and are shown in Table 3. We can interpret Table 3 as follows: The patients with liver metastases have almost four times the risk of dying from colon cancer and the risk can be in the range of two to seven times (95% CI) when compared with those without metastases. In addition, patients in Duke D or Duke C stages have, respectively, a 6-fold and 5-fold greater risk of dying than patients with Duke B stage. While those patients who received both chemotherapy and radiotherapy were at the greatest risk of dying from colon cancer compared to the other treatment modalities.

Discussion

Colon cancer is a major cancer in humans and one of the cancers with the most considerable mortality. Various studies have tried to determine the factors associated with death from colon cancer; however, findings were inconsistent and inconclusive. In this study, we analyzed a total of 115 patients with colon cancer, diagnosed and treated at the HUSM Surgical Unit, to determine the important predictors for survival status in our local setting.

The overall 5-year survival rate for colorectal cancer patients in this study (34.3%) was lower compared with the overall 5-year survival rate in developed countries such as Australia, with overall survival rates of 50% or more. However, the result is similar to a study in Bombay, India, where the overall 5-year survival rates for colon and rectal cancer were 31.2%.[15,16] At our centre, the older patients had a better 5-year survival rate (53.3%) compared with the younger age group (30.3%) in this study, similar to a study in Korea.[6] Of the 88 Malay patients in this study, 60 (68.2%) patients had died, compared with 11 (40.7%) patients from other races, resulting in a 5-year survival rate of 28.4% for Malay patients and 52.9% for non-Malays.

We found that the Dukes staging was the strongest prognostic factor in both univariate and multivariate analysis. This result was found to be consistent with those of other studies.[6,17,18] The highest HR was found to be in Dukes D patients. Nonsurgical treatment modalities (chemotherapy and/or radiotherapy) also significantly influenced the survival of patients in this study but contradicted the findings from Yeole et al[16] in his study in Bombay. In that study, patients who had not undergone treatment (39.3% of cases) were included, which is in contrast with our study where we excluded those patients. However, the small number of patients ($n = 5$) in the nonsurgical treated group yielded a wide CI for the HR (adjusted HR: 3.75; 95% CI: 1.26–11.21).

Liver metastases status was a significant prognostic factor in this study similar to the findings of another study in Japan.[15] Patients with liver metastasis had almost four times the risk of death in comparison to those without

liver metastases. Age at diagnosis had no significant influence on the risk of death in patients with colorectal cancer and is consistent with other studies.[6,8,15,19–21] However, a few studies reported that age was a significant predictor for death.[17,18]

We could not establish that tumour site was an important predictor for survival status even though Wrigley et al (2002) showed that a tumour in the rectum was a significant predictor for survival status in their multivariable method.[17] Per rectal bleeding was a prognostic factor in another study but not in our study.[22] However, that study included other symptoms such as anaemia, abdominal pain, diarrhoea, and loss of weight as well as other confounders. The combination of more symptoms to be controlled might have given different results compared with our study.

Comorbidities were not important prognostic factors; this was a similar finding to the study by Wrigley et al.[17] The ratio of patients in the three comorbidity groups for both studies was almost the same, which may have been the reason for this similarity. In addition, instead of specifying the type of comorbidity, both studies chose to simply score the number of comorbidities that the patients had regardless of the type and level of severity of the comorbidity.

In this study, the preoperative CEA level was only significantly related to survival prognosis in univariate analysis but was not an independent prognostic factor in multivariate analysis. This finding was similar to the studies by Tominaga et al (1996),[23] Hamm and Crips (1998),[24] Schwandner et al (2007),[25] but not to several other studies such as those of Park et al (1999), Wang et al (2000) and Yun et al (2007).[6,8,21] In one study, however, the preoperative CEA level was reported to be a significant prognostic factor only in the late stage of the cancer.[26]

Despite some limitations, the strength of this study can be seen from the sample size ($n = 115$), which was close to the calculated sample size (127), with average *post hoc* power of 76%.

In conclusion, Dukes staging, status of liver metastases and type of treatment are the important independent predictors for survival in patients with colorectal cancer, diagnosed and treated at the Surgical Unit, HUSM, Malaysia. Those with Dukes C staging, with the presence of liver metastases and who are treated with both chemotherapy and radiotherapy are at the greatest risk of death from colorectal cancer.

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