ORIGINAL ARTICLE

Prognostic Variables in 1814 Sporadic Colon Cancers: A Review of Experience from a Single Institution from 1999-2005

Min-Hoe Chew, *MRCS(Ed), FRCS(Ed),* Eugene Shen-Ann Yeo, *MRCS(Ed), MMed (Surgery),* Choong-Leong Tang, *MMed (Surg) FRCS (Ed), FAMS*

Department of Colorectal Surgery, Singapore General Hospital

ABSTRACT

Introduction: Singapore has one of the highest age-standardized incidence rates for colorectal cancer (CRC) at 35.1% in men and 29.9% in women which is almost double that of our neighboring Southeast Asian countries. Surgery is presently the mainstay in treatment of this cancer. This present study evaluates the clinical and prognostic characteristics of sporadic cancers treated by surgical resection in a single institution in an Asian population.

Methods: 1814 consecutive patients with CRC from 1999-2005 treated in the Department of Colorectal Surgery in Singapore General Hospital were reviewed. The clinciopathological characteristics of these patients were collected from a prospectively collected database maintained in the department since 1987. Univariate analysis was performed, and survival curves were constructed using the Kaplan-Meier method. Multivariate analysis was carried out on independent prognostic factors that were positive on univariate analysis.

Results: All patients had a minimum follow up duration of 5 years unless they were lost to follow up. There were 921 (50.8%) males and 893 (49.2%) females with a median age of 67 years (interquartile range 22-99). The predominant location of the tumour was left-sided ie distal to (and including) the splenic flexure (n=1272, 70%), and the majority presented at an advanced AJCC stage III and IV (n=1018, 56%). The most common site for solitary metastasis is in the liver (n=194, 49%) followed by the lungs (6%). Locoregional recurrence is low at 2.6% (n=46) and distant recurrence is noted at 16.8% (n=297). Disease recurrence are 5.7%, 18.1%, and 27.5% for Stages I, II and III respectively. The median five-year Cancer Specific Survival (CSS) is 58.7 % (95% CI 56.2%-61.2%). On multivariate analysis, a high pre-operative CEA , poorly-differentiated tumour grade, signet ring cell tumours, high tumour stage (T3/T4), nodal disease (N1/N2), presence of both perineural invasion and vascular emboli were all significant factors that worsened CSS.

Conclusion: Our dataset confirms the current favourable survival of colonic cancers in our country which is comparable to data from the West. Future challenges in management of patients involve improving staging, selection of high risk of recurrence of patients for closer monitoring and further adjuvant treatment to improve survival and reduce locoregional recurrence.

Keywords: Colon cancer, outcomes, prognostic factors, recurrence, survival

INTRODUCTION

With an estimated life-time cumulative incidence of around 5% and an overall long-term mortality of 40% to 50%, colorectal cancer (CRC) adds greatly to the burden to society and healthcare providers. Its rapidly increasing trend in recent decades to become the most common cancer in many countries has been attributed to environmental changes in the postwar period since the 1950s. During the period of 1968-1972, cancer of the colon was the fourth and fifth commonest cancer among men and women in Singapore respectively. In a review of data published by the Singapore Cancer Registry in 2004[1], it is now the most common primary site of cancer in men aged between 35 and 64 years, as well as a the second most common cancer in women after breast cancer. It is however the most frequent cancer when both genders are combined. (Fig.1, overleaf)

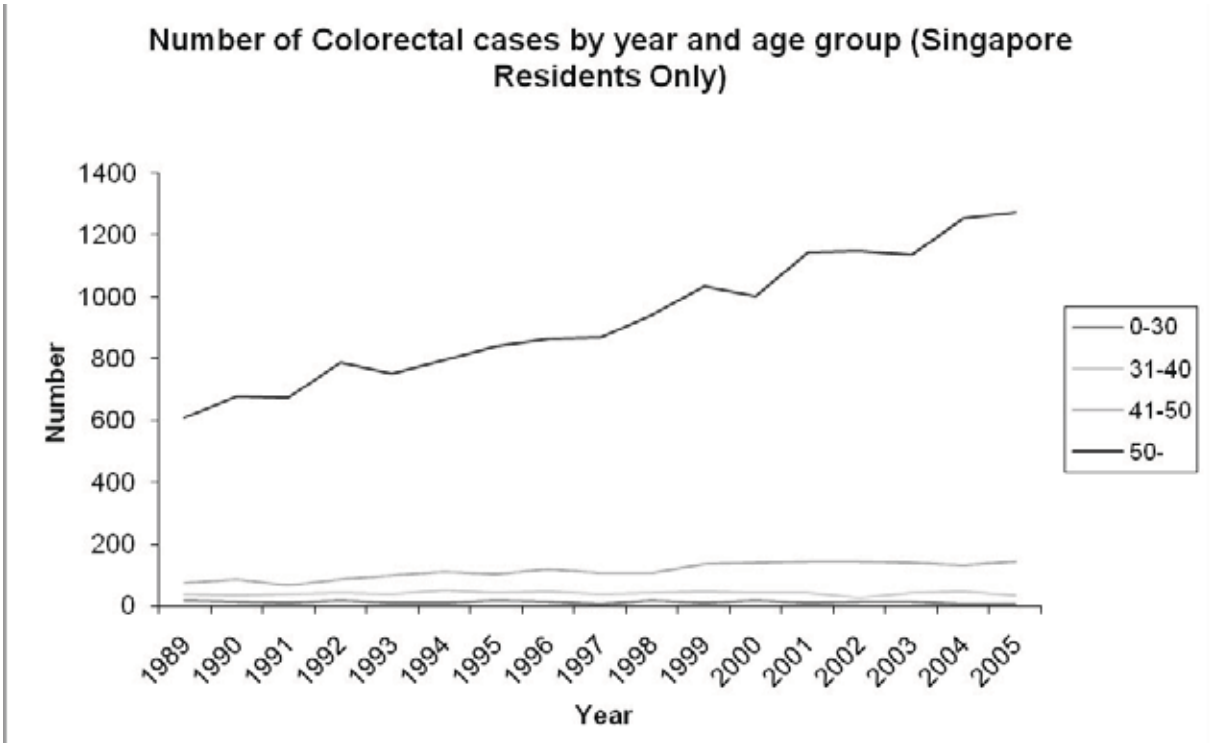

Fig. 1: Incidence of colorectal cancers in Singapore residents from 1989-2005. (Published with approval from National Registry of Diseases Office, Health Promotion Board, Singapore)

In an epidemiological review of our local data performed, Singapore has the highest age-standardized incidence rates for colorectal cancer at 35.1% in men and 29.9% in women which is almost double that of our neighboring Southeast Asian countries[2]. While these statistics are confined to Singapore Residents (citizens and permanent residents), it is consistent with various trends seen in developed nations that the probability of CRC being diagnosed is significantly higher compared to developing nations[3]. Surgical removal is currently the mainstay of treatment of the cancer. There is however little data from our local population on outcomes of sporadic colorectal cancers. This present study evaluates the clinical and prognostic characteristics of sporadic cancers managed by a single institution in an Asian population.

METHODS:

Patient Population

This study was approved by the Institutional Review Board of Singapore General Hospital (SGH). Clinicopathologic and follow up data of 1814 consecutive patients who had surgical resection for primary colon cancer from January 1999 to December 2005, were retrieved from a prospectively recorded computer database. Patients who presented with rectal cancer, recurrent cancer, Inflammatory Bowel Disease, Familial Adenomatous Polyposis and positive family history suggestive of hereditary non-polyposis colorectal cancer (HNPCC) by Amsterdam I & II criteria[4], were excluded.

Staging, Pathologic Analysis and Assessment of Recurrence

The location of the index CRC was defined as a right-sided lesion if it arose proximal to the splenic flexure. Lesions at or distal to the splenic flexure were considered left-sided. We defined a synchronous CRC as one found at the index operation for the CRC or diagnosed within twelve months after resection of the index CRC. In the case of synchronous lesions, the most advanced lesion was used for tumour stage classification comparisons. Stage of disease was evaluated by plain chest radiographs, ultrasound abdomen/liver and/or computed tomography (CT) of the abdomen and pelvis. Pathologic staging of disease was according to American Joint Committee on Cancer

Table 1. Demographics and clinicopathologic characteristics.

Factor	Category	Number of Patients (%)
Gender	Male	921 (50.8)
	Female	893 (49.2)
Age group (years)	Median (interquartile range)	67 (22-99)
	≤50	240 (13)
	>50	1574 (87)
Ethnic group	Chinese	1671 (92)
	Malay	70 (4)
	Indian	47 (3)
	Others	26 (1)
Pre-op CEA (ng/ml)	Median (interquartile range)	4.4 (0.4-21,000)
	≤5.0 ng/ml	940 (52)
	>5.0 ng/ml	785 (43)
Tumour Location	Right	542 (30)
	Left	1272 (70)
AJCC Stage	I	196 (11)
	II	600 (33)
	III	621 (34)
	IV	397 (22)
Histological subtype	Adenocarcinoma	1678 (92.5)
	Mucinous	114 (6.3)
	Signet-ring cell	22 (1.2)
Tumour differentiation	Well differentiated	195 (11)
	Moderate	1441 (79)
	Poor	157 (9)
	Not Reported	21 (1)
T stage	T1	171 (9)
	T2	1102 (61)
	T3	446 (25)
	T4	9 (<1)
	**Unclassified	
N Stage	N0	869 (48)
	N1	483 (27)
	N2	453 (25)
	**Unclassified	9 (<1)
Number of lymph nodes examined	Median (interquartile range	13 (1-58)
	<12 nodes examined	638 (35)
	≥nodes examined	1166 (65)
	**Unclassified	11(<1)
Histological characteristics	Perineural invasion - Absent	1308 (72)
	Perineural invasion - Present	310 (17)
	Perineural invasion - Not reported	196 (11)
	Vascular emboli - Absent	1241 (68)
	Vascular emboli - Present	402 (22)
	Vascular emboli - Not reported	171 (10)

Values in parentheses are inpercentages unless otherwise stated.
CEA= carcinoembroyonic antigen
** Unclassified indicates patients whereby resection was not possible

(AJCC) Staging Manual, 7th edition[5] after surgical resection with review of the resected specimen and investigations of distant metastases. Pathological examination and classification of mucinous carcinoma and signet-ring adenocarcinoma were performed in accordance with the WHO criteria[6]. Local recurrence was defined as the first clinical, radiological, and/or pathological evident tumour of the same histological type, within or contiguous to the previously treated tumour

Table 2. Types of Recurrences and metastasis.

Factor	Category	Number of Patients (%)
Metastasis (n=398)	Liver	194 (49)
	Lungs	25 (6)
	Peritoneum including ovary	69 (4)
	Others	11 (3)
	Diffused Mets	99 (25)
Recurrences (n=398)	Locoregional	46 (2.6)
	Distant	297 (16.8)
Recurrences according to AJCC stage		
AJCC I (n=11, 5.7%)	Locoregional	2 (0.6)
	Distant	9 (2.6)
AJCC II (n=106, 18.1%)	Locoregional	16 (4.7)
	Distant	90 (26.2)
AJCC III (n=226, 37.5%)	Locoregional	28 (8.2)
	Distant	198 (57.7)

Values in parentheses are in percentages unless otherwise stated

bed. Distant recurrence was defined as similar evidence of spread outside the primary tumour site at sites including but not limited to the liver, lungs, bone, brain and para-aortic region. Mortality data and the cause of death were obtained from the Singapore Cancer Registry.

Statistical analysis

All statistical analyses were performed using SPSS statistical package (version 17.0; SPSS, Chicago, Illinois). For statistical significance analysis, Pearson's chi square test and Kruskal Wallis test were performed as appropriate. In the analysis of disease free survival (DFS), a patient was considered to have an event if there was local or systemic recurrence after the completion of primary treatment. DFS was calculated from the date of surgery till the date when a recurrence first occurred. Patients with no evidence of disease after treatment were censored at the date of last follow-up. Similarly, the cancer-specific survival (CSS) was computed from the date of surgery to the date when the patient was last known to be alive. The DFS and CSS curves were constructed using the Kaplan-Meier (KM) method, and comparisons between groups of clinical interest were made using the log-rank test. Finally, a multivariate Cox regression analysis was done to evaluate the independent prognostic factors, adjusting for possible confounding factors. All statistical tests were assessed at the conventional 0.05 level of significance.

RESULTS

There were 1814 patients with CRC evaluated during the study period. 921 (50.8%) males and 893 (49.2%) females with a median age of 67 years (interquartile range 22-99). 13% (n=240) of the patients presented ≤50 years old and 90% of the cohort evaluated was Chinese reflecting the predominantly Chinese population in our country. The predominant location of the tumour was left-sided (n=1272, 70%) and the majority of the cancers presented at an advanced AJCC stage (Stage III and IV) of cancer (n=1018, 56%). (Table 1, previous page)

Subgroup analysis revealed 114 patients (6.3%) with mucinous tumours, 22 (1.2%) with signet-ring cell tumours and 1678 (92.5%) with ordinary adenocarcinomas. The majority of the lesions were moderately differentiated (n=1441, 79%) and were at an advanced T (T3/T4) stage (n=1548, 86%). 52% (n=936) of the patients had positive lymph nodes (N1/N2) at presentation and the median number of nodes examined post resection was 13 (IQR 1-58). Prognostic variable such as perineural invasion and

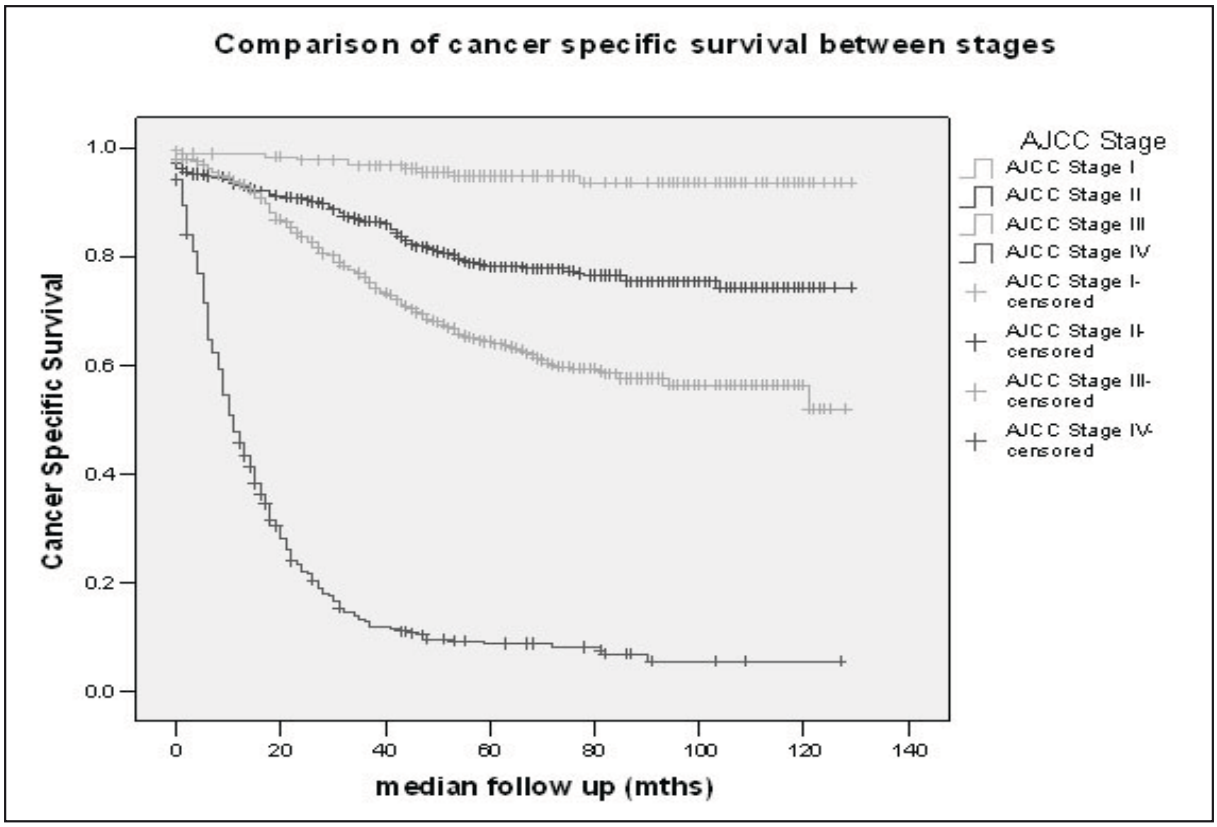

Figure 1: Comparison of cancer specific survival between AJCC Stages, p <0.0001
AJCC Stage I: 94.5% (95% CI: 91.0%-98.0%); AJCC Stage II: 76.9% (95% CI: 73.2%-80.6%); AJCC Stage III: 63.1% (95% CI: 59.0%-67.2%); AJCC Stage IV: 8.6% (95% CI: 5.5%-11.7%)

vascular emboli was reported in 17% (n=310) and 22% (n=402) respectively. (Table 1)

The site of recurrences after a curative–intent resection as well as type of metastasis on presentation is listed in Table 2. For stage IV metastasis, the most common site affecting a solitary organ is in the liver (n=194, 49%) followed by the lungs (6%). Locoregional recurrence is low at 2.6% (n=46) and distant recurrence is noted at 16.8% (n=297). Recurrences according to AJCC Stage are at 5.7%, 18.1%, and 27.5% for Stages I, II and III respectively.

On follow up, 7.7% of the patients (n=139) died from non-cancer related causes and were excluded from survival analysis. 2.7% (n=49) of the cases were lost to follow up and were also excluded from analysis. With a median follow up of 49 months (range 1-129 months), the five-year CSS is 58.7 % (95% CI 56.2%-61.2%). When the KM curves were analysed according to AJCC Stage, the 5-year CSS for AJCC Stage I is 94.5% (95% CI: 91.0%-98.0%), AJCC Stage II 76.9% (95% CI: 73.2%-80.6%), AJCC Stage III 63.1% (95% CI: 59.0%-67.2%) and AJCC Stage IV 8.6% (95% CI: 5.5%-11.7%), (Fig. 2). Comparison of DFS was also performed between AJCC Stages I-III and is illustrated in Fig. 3 (overleaf). The DFS for AJCC Stage I is 98.9% (95% CI: 97.0%-100%), AJCC Stage II is 95.1% (95% CI: 93.1%-97.1%) and AJCC Stage III is 90.1% (95% CI: 87.2%-93.0%).

On univariate analysis with log-rank test, variables like age, gender, race and site of lesion, were not significant predictors for DFS or CSS. High preoperative CEA values ≥5.0 ng/ml ($p<0.001$), moderately differentiated ($p<0.001$) and poorly differentiated tumour grade ($p<0.001$), high T-stage (T3/T4) ($p<0.001$), presence of lymph nodes (N1/N2) ($p<0.001$), presence of vascular emboli ($p<0.001$) as well as perineural invasion ($p<0.001$) were predictors for recurrence of disease as well

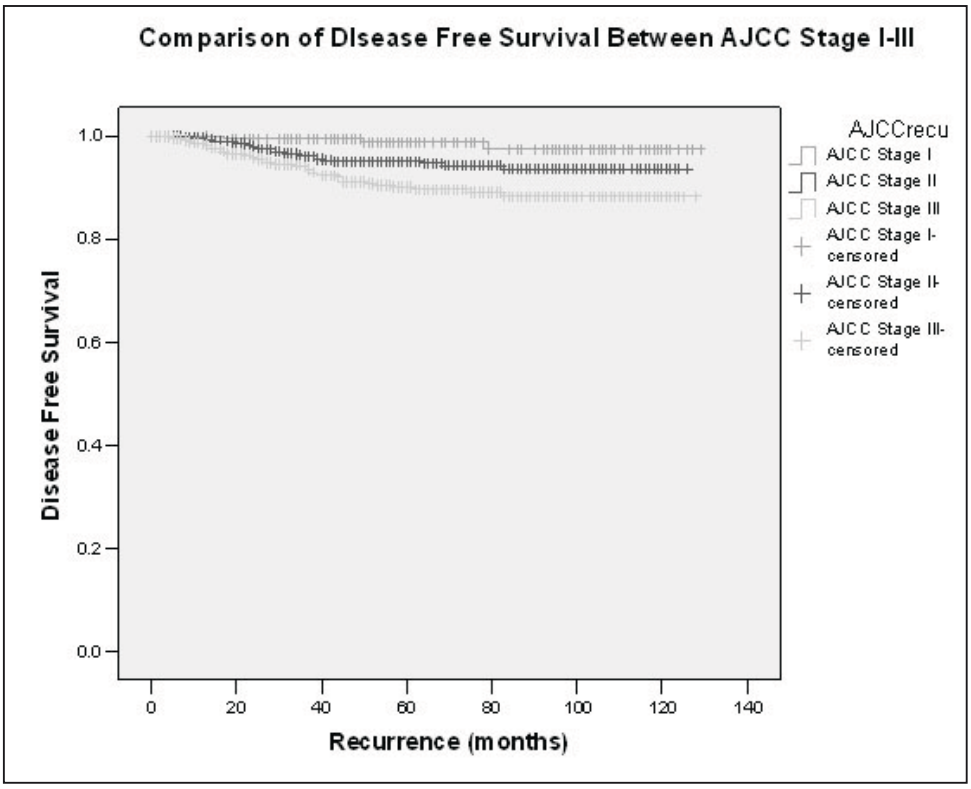

Fig 3 Comparison of Disease Free Survival between AJCC Stages I-III, **p<0.0001**
AJCC Stage I: 98.9% (95% CI: 97.0%-100%); AJCC Stage II: 95.1% (95% CI: 93.1%-97.1%); AJCC Stage III: 90.1% (95% CI: 87.2%-93.0%

as risk factors for poor cancer specific survival on univariate analysis. (Table 3) To adjust the curves for any other factors that might have influenced overall survival of the cohort, we used the Cox proportional hazards model in a forward-stepwise manner to analyze covariates of CEA, tumour grade, histological subtype, T-stage, N-stage, perineural invasion and vascular emboli. From our analysis, a high CEA, poorly-differentiated tumour grade, signet ring cell tumours, high tumour stage (T3/T4), nodal disease (N1/N2), presence of both perineural invasion and vascular emboli were all significant factors that worsened cancer-specific survival. (Table 4) Moderately differentiated tumours and mucinous lesions however, did not worsen survival.

DISCUSSION

Global estimates suggest that colorectal cancer trends will continue to rise worldwide with an estimated 15 million new cases by year 2020[3]. This trend in Singapore is likely to continue to rise as well and recent unpublished estimates from Singapore Cancer Registry demonstrate this rising incidence in all age groups. (Fig.3) In spite of this dramatic rise, there has been significant progress in the survival of patients afflicted with CRC. In an epidemiological review performed by Du et[7] in 2002, 5-year age standardized relative survival figures for colon cancer was noted to improve from 32 to 71% in women and 36 to 66% in men in the period from 1968 to 2002. This improved survival has been attributed to overall improvements in national socio-economic and health care services, as well as the utility of improved treatment guidelines and therapeutic protocols. In addition, the development of specialized tertiary care centers in colorectal complemented by National Cancer Centres with wide ranging facilities in diagnosis and adjuvant treatment, together provide current and advanced curative and palliative treatment for CRC[8].

Data from our own experience demonstrates a 5-year survival at 58.7% which is largely similar to the current data reported by the American Cancer Society at 61.1%[9]. Poor prognostic factors noted in our series consists of high CEA, poorly-differentiated

Table 3. Univariate analysis of patient and tumour factors influencing Cancer Specific Survival.

Variable	Cancer Specific Survival	
	Hazard Ratio (95% Confidence Interval)	**P value**
CEA (ng/ml) <5.0 **≥5.0**	1.0 **2.7 (2.4-3.2)**	**p<0.001**
Age (years) <50 ≥50	1.0 <1.0	p=0.754
Right vs left sided lesions Right Left	1.0 1.0	p=0.669
Tumour Grade Well **Moderate** **Poor**	1.0 **2.1 (1.5-3.1)** **5.4 (3.6-7.9)**	 **p<0.001** **p<0.001**
Histological subtype Adenocarcinoma Mucinous **Signet-ring cell**	1.0 1.2 (0.9-1.6) **5.1 (3.2-8.0)**	 p=0.197 **p<0.001**
T stage T1/T2 **T3/T4**	1.0 **5.2 (3.6-7.7)**	**p<0.001**
N stage N0 **N1/N2**	1 **3.3 (2.8-4.0)**	**p<0.001**
Vascular emboli No **Yes**	1.0 **3.4 (2.9-4.0)**	**p<0.001**
Perineural invasion No **Yes**	1.0 **3.1 (2.6-3.7)**	**p<0.001**

Table 4. Multivariate analysis of patient and tumour factors influencing Cancer Specific Survival.

Variable	**Cancer Specific Survival**	
	Hazard Ratio (95% Confidence Interval)	**P value**
CEA (ng/ml) <5.0 **≥5.0**	1.0 **2.2 (1.8-2.6)**	**p<0.001**
Tumour Grade Well **Moderate** **Poor**	1.0 **2.1 (1.5-3.1)** **5.4 (3.6-7.9)**	 **p<0.001** **p<0.001**
Histological subtype Adenocarcinoma Mucinous **Signet-ring cell**	1.0 1.2 (0.9-1.6) **5.1 (3.2-8.0)**	 p=0.197 **p<0.001**
T stage T1/T2 **T3/T4**	1.0 **5.2 (3.6-7.7)**	**p<0.001**
N stage N0 **N1/N2**	1 **3.3 (2.8-4.0)**	**p<0.001**
Vascular emboli No **Yes**	1.0 **3.4 (2.9-4.0)**	**p<0.001**
Perineural invasion No **Yes**	1.0 **3.1 (2.6-3.7)**	**p<0.001**

tumour grade, signet ring cell tumours, high tumour stage (T3/T4), nodal disease (N1/N2), presence of both perineural invasion and vascular emboli. These have been reported in other series as well. In our local population, we have also noted that young age[10] and the presence of mucin[11] are not significant poor prognostic variables and do not worsen survival. In general, consensus guidelines[9] have recommended surgical treatment alone for AJCC Stage I disease and surgery plus adjuvant chemotherapy for Stage III disease. Adjuvant therapy for Stage II and IV however is much less uniform and indications and regimes are varied. In particular, selection of patients for systemic adjuvant therapy remains controversial for stage II CRC. In a recent Cochrane database review in 2008, although pooled analysis of randomized controlled trials have not demonstrated a proven survival benefit for adjuvant chemotherapy in stage II colon cancer, there seems to be an improved disease-free survival with adjuvant therapy[12]. It is possible that clinicians are thus more inclined to administer adjuvant chemotherapy in the presence of poorer prognostic factors. This can occur especially in the younger patient as they have less co-morbidities and are more likely to tolerate the toxicities associated with chemotherapy. At this current point in time, adjuvant systemic chemotherapy is offered in stage II patients who have high risk features, including obstruction, perforation, inadequate lymph node sampling or T4 disease[12]. Our multivariate analysis may define additional high-risk features in stage II colon cancer patients which may be used to select patients for adjuvant

therapy in our local population. Nonetheless, co-morbidities and likelihood of tolerating adjuvant systemic chemotherapy should be considered in the discussion with the patient. In addition, efforts should persist to develop other therapies which might be more effective, shorter in duration and less toxic than those available today.

Despite the improved survival over the years, one of the important findings in this study is that the majority of the lesions are still diagnosed at an advanced AJCC stage of disease (56%). Evidently, many challenges in the management of CRC remain in our country. Considerable efforts to evaluate effective screening tests to detect CRC at early curable stages have been made worldwide. Screening by FOBT has proven to be effective in decreasing mortality from CRC. A recent review by the Cochrane Library comprising of subjects enrolled in four randomized controlled trials exceeding 320,000 and an average follow-up period ranging from 8 to 18 years, concluded that FOBT screening has led to a reduction in CRC mortality of 16% [Relative risk (RR) 0.84, 95% confidence interval (CI) 0.78-0.92]. When adjusted for screening attendance, the reduction rises to 25% (RR 0.75, CI 0.66-0.84)[13]. Several efforts have been used to promote screening in our country. In a mass screening event organized in which immunochemical quantitative FOBT (QFOBT) kits were issued, there were 1048 participants who attended. In this cohort, 49 participants (26 males, 23 females) tested positive for QFOBT and 47 were evaluated. 22 percent (n=10) had polyps and one colorectal cancer was detected. Seven of these cases had significant neoplasia (lesions ≥ 1cm) and two of these patients required surgery[14]. These results provide further evidence of the importance of screening with potential reduction in CRC mortality. Continual education of the public in events like these, are essential to improve attitudes towards screening. And with government efforts to promote and encourage CRC screening, these may lead to improved survival in the near future.

In addition, current surgical management of colonic and rectal cancer has already taken on a whole new dimension. To date, laparoscopic colectomy has gained popularity in the surgical management of both benign and malignant colorectal diseases over the years and has become the preferred choice. The benefits reported include a shorter median hospital stay, reduced usage of parenteral narcotics and oral analgesics, as well as morbidity and have been described in large scale multi-centered randomised studies[15–18]. Importantly, oncological outcomes are achieved as effectively with laparoscopic surgery compared to conventional open surgery[19]. Long term outcome in terms of lymph node harvest, specimen length as well as long term overall survival has also been shown to be equivalent to open surgery as suggested by a recent Cochrane database review in 2008[20]. Laparoscopic colectomy has been similarly embraced in our department and we have demonstrated good outcomes in our early experience[21,22]. While we await long term results, it is expected to demonstrate similar advantages. Thus, unless there are patient contraindications, laparoscopic colectomy has become the surgical procedure of choice in the surgical management of colorectal cancer.

CONCLUSION:

Despite the limitations of a retrospective review as ours, our dataset confirms the current favourable survival of colonic cancers in our country which is comparable to data from the West. And with the dramatic increase in incidence expected in the years to come, there is an urgent need for us to utilize valuable information obtained over the years to improve detection, surgical management as well as adjuvant treatment. The continued unraveling of molecular pathogenesis of CRC offers impetus to improvements in genetic testing, patient selection for adjuvant therapy based on various immunohistochemical parameters, as well as improves awareness and possible utility of various targeted molecular therapeutics. Further challenges lie ahead for both surgeons and physicians alike in the future management of colorectal cancer.

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