COLORECTAL CANCER;
OVERALL SURVIVAL AND ITS PROGNOSTIC FACTORS, A RETROSPECTIVE ANALYSIS FROM 10 YEAR DATA FORM JHL

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ABSTRACT... There is paucity of data on epidemiology and survival in colorectal cancer from developing countries. **Objectives:** To determine overall survival and its predictive factors. **Setting:** Department of Oncology Jinnah Hospital Lahore. **Period:** From July 1997 to Dec 2007.**Methods**: 73 patients were analyzed. Patient demographic data including age, sex, socio-economic status, pre-treatment CEA levels, Duke's stage, site of tumor (colon, rectum) and complete tumor resectability were recorded. Univariate analysis by chi-square and multivariate analysis were performed by Cox Regression Model to evaluate the predictors of survival. SPSS v 13.0 was used for statistical analysis. Kaplan-Meier estimate was used to calculate survival. **Results:** Median age of our patients was 45 years. Male to female ratio was 1:1.2. Complete surgical resection could be performed in only 48 (68.5%) patients. Majority (70%) patients had Duke C and D. Overall survivals at 36 months was 53 % and was 90% for Duke A and B, while it was 61% and 26% for Duke's C and D respectively. Females had a better survival rate of 74% as compared to males with a survival of 36%. Patients with proximal colon tumors had survival of 73% as compared to 37% in rectal/recto-sigmoid group. Patients with high pre-treatment CEA had poor survival 39%. Only 25% patients with unresectable tumors were alive at 36 months compared to 67% in patients with resectable tumors. Conclusion: Significant predictive factors for improved survival were female gender, early disease, patients with proximal colon tumors, low pre-treatment CEA levels and complete tumor resection.

Key words: Colorectal Cancer, survival, prognostic factors, developing countries

INTRODUCTION

Colorectal cancer has traditionally been one of the most commonest malignancies in the western population. However, during past few decades, there has been a remarkable increase in the incidence of colorectal cancer in Asian countries[1, 2].

It is also one of the frequently encountered malignancy in the Northern region of Pakistan and ranked among first 10 malignancies in both sexes according to population based tumor registry in Karachi [3,4,5].

In the developed countries, advances in the management of colon cancer and its detection at an early stage over past decade has resulted in improvement of 5 years survival, which now stands at 90% for localized disease. Survival for other categories is 64% with regional lymph node or surrounding structures involvement and only 8% for metastatic disease[6, 7].

Various prognostic factors such as age, gender, pre-surgical CEA levels, site of disease, histological feature, obstruction or perforation and perioperative blood transfusions etc. have been described in literature[8,9,10,11]. On the other hand, after resection only stage of the disease and grade of the tumor have been consistently correlated with overall survival[6]. Han Liang from China also reported the worse effect of the gross residual disease after surgery on overall survival[12]. Domestic studies have laid main emphasis on epidemiology and clinical pathology.

This study was conducted to determine the overall survival and to identify its prognostic factors in patients with colorectal carcinoma, presenting in the Department of Oncology, Jinnah Hospital Lahore, Pakistan.

STUDY DESIGN
Patients
Data from 73 patients presenting from July 1997 to December 2007, with a diagnosis of colorectal cancer, was retrospectively analysed in this study. Patients with Gastro-intestinal Lymphomas and Gastro-intestinal Stromal Tumor (GIST) were excluded from the study population. Patient with Duke's C and high risk Duke's B were given adjuvant chemotherapy whereas the patients with Duke's D tumors received the palliative chemotherapy. Patients with rectal cancers were also given radiation-chemotherapy.

Statistical Analysis
Overall survival was calculated from the date of diagnosis to the last follow up or death due to any cause. SPSS 13.0 was used for statistical analysis. Survivals were estimated by using Kaplan-Meier estimates and the two survival curves were compared a log-rank test. A Cox-Regression Model Analysis was performed to evaluate different variables associated with survival. The variables included were age, gender, socio-economic status, grade of the tumor, and Duke's stage at presentation, number of lymph nodes involved, primary site of the tumor, pre-treatment CEA levels and tumor resectablity.

RESULTS
Characteristics of 73 patients are given in Table-I.

Table-I. Base line characteristics of the patients	
Characteristic	N = 73(%)
Age-Yrs Median Range	45 15-85
Gender Male Female	39 (53.4) 34 (46.6)
Socio-Economic Status Low Middle High	48 (65.8) 22 (30.1) 03 (4.1)
Symptoms at Presentation Pain abdomen Abdominal distension Bleeding P/R Altered bowel habits Intestinal obstruction	60 (82.2) 21 (28.8) 34 (46.6) 50 (68.4) 14 (19.2)
Family History Colorectal cancer Breast cancer Hepatocellular cancer	7 (9.6) 1 (1.4) 2 (2.7)
Tumor Site Colon Rectum/RSJ	46 (63) 27 (37)
Histopathology Adenocarcinoma SCCA	69 (94.5) 4 (5.5)
Grade of Tumor Well differentiated Moderately differentiated Poorly differentiated	23 (31.5) 37 (50.7) 13 (17.8)
DUKE'S STAGE A&B C D Pre- Treatment CEA (ng/dl) High Low NA	21 (28.8) 30 (41.1) 22 (30.1) 30 (41.1) 25 (34.2) 18 (24.7)
Post-Treatment CEA (ng/dl) High Low NA	11 (15.1) 27 (37) 35 (47.9)
Surgery Resection and ETE anastomosis APR Hartman's Procedure Loop colostomy/Biopsy only None	31 (42.5) 14 (19.2) 5 (6.8) 17 (23.3) 6 (8.2)

SCCA = squamous cell carcinoma; CEA = chorioembryonic antigen; ETE = end – to – anastomosis; APR = abdomino – perineal resection; 5 FU = 5fluorouracil; FA = folinic acid; CDDP = cisplatin; FOLFOX = folinic acid, fluorouracil, oxaliplatin; FOLFIRI = folinic acid, fluorouracil, irinotican;

CR = complete response; PR = partial response

Median age of patients was 45 years (15- 85) and 24 (33%) were younger than 40 years. Male to female ratio was 1: 1.2. Median follow-up was 11 months (2- 108). Majority of the patients 48 (65.8%) belonged to poor socio-economic group. 52 patients (70%) presented with advanced stage (Duke C and Duke D). Proximal colon was involved in 46 (63%) patients while 27 (37%) patients had tumor in the rectum as recto-sigmoid junction. Rectal cancers were more common in males, 41% as compared to 29% in females. Unresectable tumors were found in 26 (36%) patients. Duke's D unresectable tumors were more common in males, 41% Vs 22% of colon cancer. Preoperative high CEA levels were found in 41% patients.

COX-Regression analysis for survival is shown in Table- II.

| Table-II Cox-Regression Analysis for Overall Survival (OS) in Colorectal Cancer (CRC)			
Factors	N(%)	HR (95% CI)	P-value
Age, years			
≤40	39 (53.4)	1	0.8
>40	34 (66.7)	1.08(0.39-2.9)	
Gender			
Male	39 (53.4)	1	0.0.4
Female	34 (46.6)	0.3 (0.09-0.95)	
Socio-economic Status			
Low	48 (65.8)	1	0.1
Middle/High	25 (34.2)	2.28(0.73-7.17)	
Tumor site			
Colon	46 (63)	1	0.1
Rectum/Sigmoid	27 (37)	2.97(1.09-8.08)	
Grade of tumor			
WD/MD	60 (82.2)	1	0.03
PD	13 (17.8)	1.04(0.36-2.98)	
Nodes involved	(n=46)		
None	12 (16.4)	1	1
yes	34 (72.7)	1.23(1.02-1.45)	
Duke's Stage			
A&B	21 (28.8)	1	
C	30 (41.1)	3.35(0.37-30.06)	
D	22 (30.1)	12.6 (1.64-97.5)	0.01
Pre-treatment CEA (ng/dl)	(n=55)		
High	30 (54.4)	1	0.05
Low	25 (45.6)	0.25 (0.06-1.08)	
Resectablity of tumor	51 (69.8)	1	0.01
Resectable Unresectable	22 (30.2)	3.41 (1.29-9.01)	

At 36 months overall survival was 53%, stage wise survival is shown in figure-I. 36 months overall survival was 90% in Duke`s A and B, while 61% for Duke`s C and 26% for Duke`s D stage. Females had better a three years survival of 74% as compared to 36% in males (P-value 0.04). There was no statistically significant survival

difference between patients $\leq$ 40 years of age and older patients (P-value 0.8). Patients with colonic cancer had better 36 months survival of 73% as compared to 37% in patients with rectal or rectosigmoid junction tumors (P-value 0.03).

Figure 1: Overall survivals in colorectal cancer. (A) Overall survival (B) Duke's stage (C) Gender (D) Tumor site (E) Tumor resectablity (F) Pre-treatment CEA levels.

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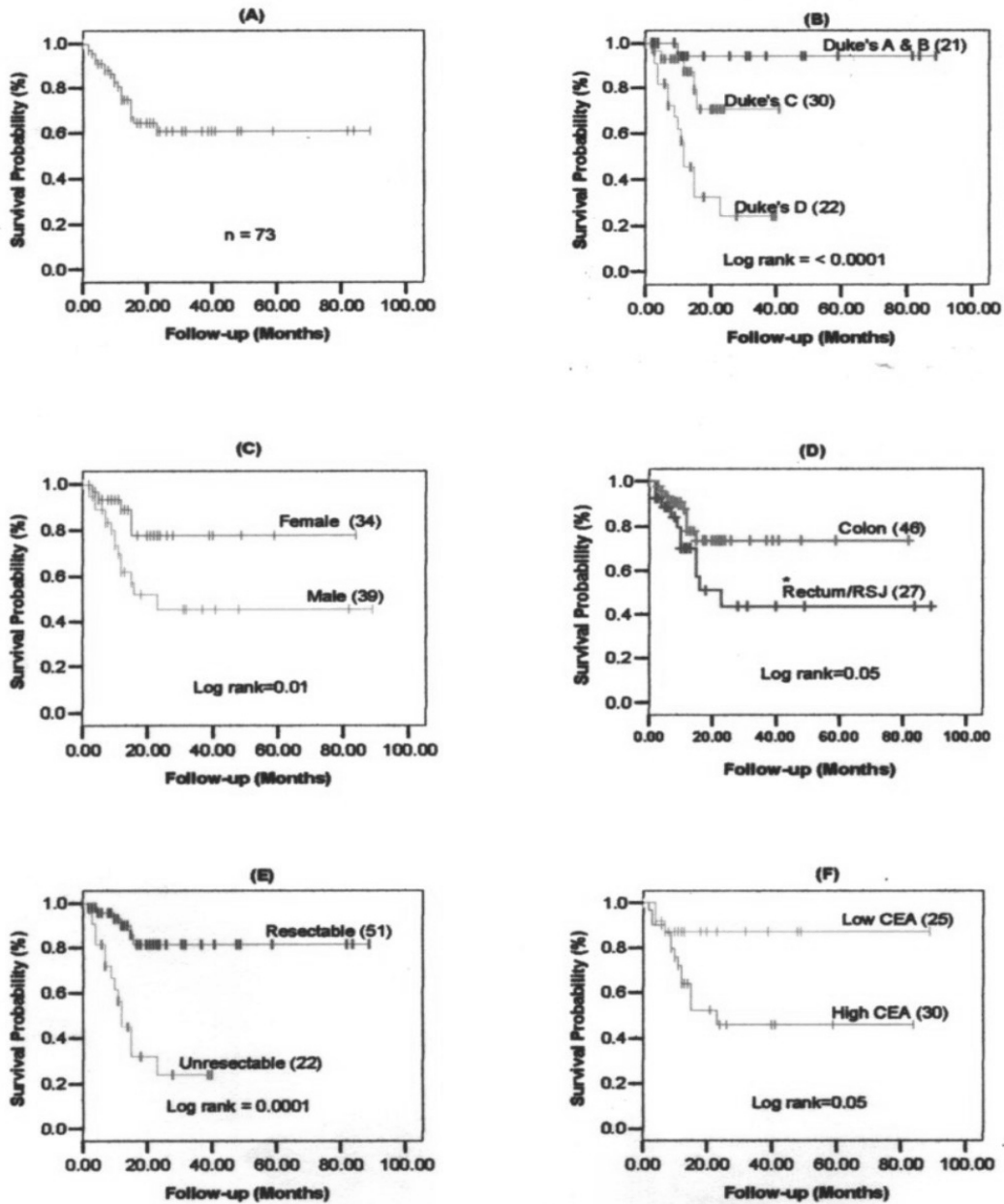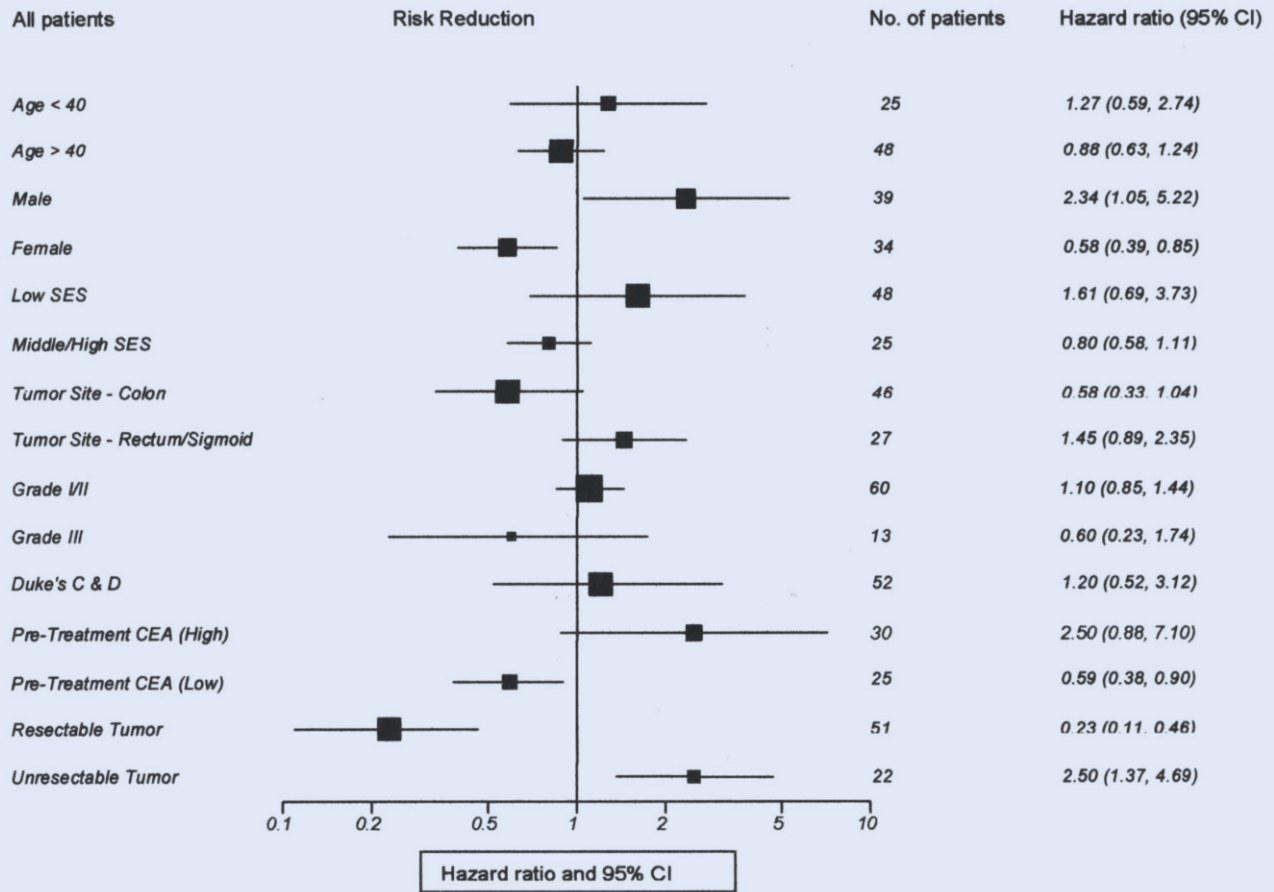

* RSJ = recto-sigmoid junction
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tients with unresectable tumor had significantly inferior survivals of 25% as compared to 66% in patients with resectable tumor (P-value 0.01 on COX regression analysis). Patients with raised pre treatment CEA had

poor survival of only 39% and were alive at 36 months compared to 86% of patients with low or normal CEA level (P-value 0.05).

Figure 2: Forest Plot Analysis of prognostic and predictive factors for overall survival by different subgroups.

All patients	Risk Reduction	No. of patients	Hazard ratio (95% CI)
Age < 40		25	1.27 (0.59, 2.74)
Age > 40		48	0.88 (0.63, 1.24)
Male		39	2.34 (1.05, 5.22)
Female		34	0.58 (0.39, 0.85)
Low SES		48	1.61 (0.69, 3.73)
Middle/High SES		25	0.80 (0.58, 1.11)
Tumor Site - Colon		46	0.58 (0.33, 1.04)
Tumor Site - Rectum/Sigmoid		27	1.45 (0.89, 2.35)
Grade I/II		60	1.10 (0.85, 1.44)
Grade III		13	0.60 (0.23, 1.74)
Duke's C & D		52	1.20 (0.52, 3.12)
Pre-Treatment CEA (High)		30	2.50 (0.88, 7.10)
Pre-Treatment CEA (Low)		25	0.59 (0.38, 0.90)
Resectable Tumor		51	0.23 (0.11, 0.46)
Unresectable Tumor		22	2.50 (1.37, 4.69)

Hazard ratio and 95% CI

DISCUSSION

Colorectal cancer is a disease of elderly, the median age of affected patients in USA is 72 years [6]. The median age of patients in current study is low, same is shown in other studies from Pakistan and neighboring countries [3,4,12,13,14]. This can partially be explained by short life expectancy in developing countries, where the main bulk of population is in the range of 15-64 years of age [3]. Although age did not emerge as prognostic factor but studies from the West and China have reported young age as poor

prognostic factor for overall survival [9,10,15,16,17]. probably because of late stage, prevalence of high grade, poorly differentiated or mucinous histology in younger patients at the time of presentation. Nadra Mamoon from Northern Pakistan has also reported advanced stage and poorly differentiated histology in younger patients, however studies did not find any survival difference in different age groups [3,12,18,19]. On the other hand studies from India and Malaysia reported poor survivals in elderly, so there may be variation in tumor behavior in

different age groups in different geographical regions.

Location of tumor is one of the prognostic factors for survival. Patients with colon cancer have better survival as compared to those with rectal cancer [18,20]. In this study rectal and rectosigmoid junction tumors were also associated with inferior survivals than with rest of colon probably because of prevalence of advanced and unresectable cancer in rectum. 52% of rectal cancers were found to be advanced and unresectable as compared to 22% in rest of colon. Rectal cancers usually present with bleeding per rectum and these symptoms can easily be disregarded by the patients because hemorrhoids are quite common in our population[6]. Whether poor survival in patients with rectal and rectosigmoid junction is due to the aggressive biological behavior or its closed proximity to other structures in pelvis which may make complete resection difficult, needs further workup.

Female gender was found to be good prognostic factor consistent with study from abroad[20]. It is difficult to explain the reason for better survival in females but it can be partially explained by the fact that rectal and advanced stage unresectable tumors were less common in female patients as compared to males.

Advanced stage (Duke C and D) at presentation and unresectability emerged as most significant prognostic factors consistent with findings of other studies [8,12,14]. Advanced stage is interlinked with unresectability, as shown in a study from China, which demonstrated poor survival for patients having gross residual disease after surgery[12]. So it is prudent to diagnose colorectal cancer at the stage when complete resection is possible. Majority, (70%) of patients in this study presented at advanced stage, which not only reflects the lack of awareness and health education in our population (not taking alteration in bowel habits seriously) but also a poor access to health facilities, which results in delayed referral and diagnosis at specialized center for cancer treatment.

Survivals in our patients in this study cannot be compared with those reported in literature because of short median follow up. For concrete results further follow up is required. To achieve equivalent survival with the West, we need health education in our masses as well as in primary health care givers, screening program for early detection with availability of diagnostic facilities and improvement in surgical skills.

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People are to be loved and things are to be used... Immorality occurs, when things are loved and people are used.

Anonymous