Pathology and Prognosis of Colorectal Cancer

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Abstract

Introduction: Colorectal cancer (CRC) is one of the most common cancers in the world. During the past decades, survival of colorectal cancer patients has improved worldwide, however, it is not clear what factors have contributed to this development. This study was designed to evaluate the prognostic impact of a wide spectrum of pathologic parameters on survival rate in patients with colorectal cancer.

Methods: 1127 patients with colorectal cancer who registered in one cancer registry in Iran were followed from their diagnostic date to Jan 1, 2007 (as failure time). Overall survival time was calculated by Kaplan-Meier method. The Cox proportional hazard model was used to identify the pathologic factors that could independently influence survival.

Results: The overall survival rate at 5 years after diagnosis was 61%. Histology grade, status of regional lymph node metastasis, distant metastasis and pathologic tumor stage were related to survival rate according to univariate analysis. Nevertheless, in multivariate analysis, only histology grade, distant metastasis and tumor size had influence on survival of colorectal cancer patients.

Conclusion: Generally the prognosis of disease is not poor; however, distant metastasis, poor differentiation and higher tumor size should be considered to have additional risks of death in colorectal cancer.

Keywords: pathology, prognosis factors, colorectal cancer

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Introduction

Cancer is an important problem in both public health and political terms worldwide [1] . Colorectal cancer (CRC) is one of the most common cancers and is the second leading cause of cancer death in men and women in the United States [2, 3]. There is an increase in CRC incidence due to westernization of lifestyle in the recent years [1]. There are nearly one million new cases of CRC diagnosed world-wide each year and half a million deaths [3]. According to Iranian annual national Cancer Registration Report, CRC is the third common cancer in women and the 5th in Iranian men [4]. The incidence of CRC has been increased during the last 25 years [5]. In one study, Cumulative 1–5 year prevalence in the whole Iranian population had been estimated 19.66 per 100000 [6].

During the past decades, survival of CRC patients has improved [7,8] worldwide ;however, it is not clear what factors have contributed to this development [9]. Prognosis in patients with CRC is determined by the tumor itself as well as certain patient-related factors. Knowing the prognostic factors could therefore help the physicians to improve prognosis [10]. Pathoclinical characteristics of tumor and many other prognostic factors have impact on survival time. This study was designed to evaluate the prognostic impact of a wide spectrum of pathologic parameters on survival rate in patients with colorectal cancer.

Materials and Methods

Data on all colorectal cancer patients who registered in the cancer registry center of Research Center of Gastroenterology and Liver Disease (RCGLD) of Shahid Beheshti Medical University; Tehran, Iran between Jan 2002 to Jan 1, 2007 were reviewed and analyzed. This center is a referral center for GI cancer, and patients refer to this cancer registry from public and private hospitals. All patients were followed from their diagnostic date until Jan 1, 2007 (as failure time). The survival of the patients was calculated from the time of pathology report.

In this study, we used existing data and demographic and clinicopathological factors were gathered using pathology reports registered in cancer registry forms. The parameters which could be associated with survival were gender, age, extent of wall penetration, status of regional lymph node

Table 1: *Pathological Characteristics of patients with colorectal cancer*

Variable		Frequency	
		n	%
Age at diagnosis(yrs) (n=1127)	<50	482	42.8
	>50	645	57.2
Sex(n=1127)	Male	690	61.2
	Female	437	38.8
Histology grade(n=798)	Well differentiated	443	39.3
	Moderately differentiated	285	25.3
	Poorly differentiated	70	6.2
Extent of wall penetration(n=940)	Without penetration	119	10.6
	With penetration	821	72.8
Regional lymph node metastasis(n=850)	Absent	438	38.9
	Present	412	36.6
Distant metastasis(n=766)	Absent	595	52.8
	Present	171	15.2
Pathological stage(n=971)	Early	438	38.9
	Advanced	533	47.3
Location of primary tumor(n=1108)	Colon	748	66.4
	Rectosigmoid	100	8.9
	Rectum	260	23.1
Tumor size(n=1127)	<25mm	81	7.2
	>25mm	1046	92.8
Histology type(n=1127)	Adenocarcinoma NOS	872	77.4
	Signet cell car. &mucin-producing adeno. & mucinous adeno.	146	13.0
	Other type of histology	109	9.7

metastasis, distant metastasis, histological grade, pathological stage, location of the primary tumor, histologic type and tumor size.

Pathologic stage was defined as early stage (0,IA,IB,II,IIA,IIB) and advanced stage (IIIA,IIIB,IV) according to the TNM classification . Location of primary tumor was divided in to three categories: (1) colon, (2) rectosigmoid and (3) rectum. In addition, histology type of tumor was defined as (I) Adenocarcinoma, Not Otherwise Specified (NOS), (II) Signet Cell Carcinoma and Mucin-producing adenocarcinoma , Mucinous adenocarcinoma and (III) other type of histology.

Survival time was calculated from the date of diagnosis to the date of death or last follow-up. The relationship between pathologic variables and survival was estimated using Kaplan-Meier method [11]. Differences among the survival curves were tested for statistical significance with the help of the log-rank test. The Cox proportional hazard model [12] was used to identify the pathologic factors that could independently influence survival. Survival time was calculated in months. $P < 0.05$ was considered as significant.

Results

Of the 1127 cases reviewed, a male preponderance was observed (61.2% males versus 38.8% females). Median age was 53 years (range 14–94). Histologically, adenocarcinoma was observed in 77.4% of the patients. Staging was primarily pathological; early stage was observed in 38.9% of the cases, and advanced stage in 47.3% of all the cases at the time of diagnosis. The most common site of tumor was at colon (66.4%) (Table1). The mean survival was 104.99 months (CI 95%:94.96-115.01). The overall 5-year survival was 61.0%.

Univariate analysis of the prognostic factors revealed that histology grade, status of regional

Table 2: *Prognosis factors in colorectal cancer patients using Kaplan – Meier methods*

Variable		Survival mean (month)	P-value
Histology grade(n=796)	Well differentiated	113.773	0.009
	Moderately differentiated	74.458	
	Poorly differentiated	71.051	
Lymph node metastasis(n=847)	Absent	106.543	0.022
	Present	101.179	
Distant metastasis(n=765)	Absent	121.670	<0.0001
	Present	72.088	
Pathological stage(n=968)	Early	118.755	0.002
	Advanced	90.310	

Table 3: *Independent prognosis factors by Cox proportional hazard model*

Variable		Hazard ratio	P-value
Histology grade	Well differentiated*	1	-
	Moderately differentiated	1.77	0.006
	Poorly differentiated	2.05	0.029
Distant metastasis	Absent*	1	0.006
	Present	1.99	
Tumor size	<25mm*	1	0.029
	>25mm	3.61	

*Reference group

lymph node metastasis, distant metastasis and pathologic tumor stage were significantly correlated to a worse survival (Table 2). No significant association was observed between age at diagnosis (p=0.268), sex (p=0.288) , extent of wall penetration (p=0.125), size of tumor (p=0.066), location of primary tumor(p=0.936) and histology type (p=0.88) and survival of patients.

In Cox proportional hazards model analysis, histology grade, distant metastasis and tumor size were significant independent factors predicting 5-year cancer-specific survival (Table 3).

The following variables were not of prognostic significance in relation to survival using cox proportional hazard model: extent of wall penetration (P = 0.817); status of regional lymph node metastasis (p= 0.732) and pathological stage of tumor (p= 0.747).

Discussion

Data analysis showed that about 61% of patients survive 5 years after diagnosis and many pathologic factors affect their prognosis.

In the present study, the stage of tumor was correlated to worse survival. The 5-year survival rate for patients with CRC is largely dependent on TNM stage. The TNM staging system was initially developed to predict prognosis; however, its function has expanded to aid in the choice of treatment and in the selection of patients for clinical trials [13, 14].

Histologic grade of tumor, as expected, is a highly superior prognostic discriminator in both univariate and multivariate studies. Mismatch repair status is now considered an important potential prognostic factor. It is also known that microsatellite unstable CRCs are more poorly differentiated and tend to be more frequently mucinous (which by definition are poorly differentiated). Though tumor grade is found in this study to have independent prognostic value, this could be an effect of MSI rather than of tumor grade itself [15].

In the present study, the state of regional lymph node metastasis was a highly significant independent prognostic factor like the others [16-18]. Data on the incidence and risk factors of lymph node metastasis in patients with T1 or T2 cancers are important particularly when limited resection without adequate lymphadenectomy is considered [19].

Among the pathological factors, survival difference was not observed according to the histology type of tumor. This result is consistent with some studies [20, 21]. The diameter of tumors is also

a prognostic factor. Results of the present study showed that patients with tumor size lower than 25 mm have higher survival rate than other patients with tumor size > 25 mm ; this finding was also in accordance with other studies [22,23].

Many studies indicated that there was a relationship between extent of wall penetration and prognosis [19, 24]. The results of univariate analysis in the present study have also confirmed these findings.

Cox proportional hazard model revealed that distant metastasis was a significant independent factor predicting poor survival. There are many reports that confirm our findings [24-27].

This study has some limitations: for example, we used existing data and we had no access to other important information like the percentage of non resected primitive tumours or metastases, the proportion of endoscopic resections, the location and number of metastasis, the number of examined lymph nodes and etc. The mentioned data could influence the prognosis of colorectal cancer.

In conclusion, Prognosis of disease is not generally poor ; however, distant metastasis, poor differentiation and higher tumor size should be considered to have additional risks of death in colorectal cancer. Further studies are needed to determine the role of the various clinical and pathologic factors in CRC prognosis.

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