

Pathology and Prognosis of Colorectal Cancer

Safaei A¹, Moghimi-dehkordi B¹, Fatemi SR¹, Ghiasi S¹, Zali MR¹

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

1. Research Center for Gastroenterology and Liver Disease, Shahid Beheshti University (M.C)

Corresponding Author :
Azadeh Safaei
Tel: ++98-9329458217
Fax: ++98(21)22432517
Email: azadesafaei@yahoo.com

IJCP 2009; 3: 137-141

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 into 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
	Moderately differentiated	74.458
	Poorly differentiated	71.051
Lymph node metastasis(n=847)	Absent	106.543
	Present	101.179
Distant metastasis(n=765)	Absent	121.670
	Present	72.088
Pathological stage(n=968)	Early	118.755
	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
	Poorly differentiated	2.05
Distant metastasis	Absent*	1
	Present	1.99
Tumor size	<25mm*	1
	>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.

Acknowledgments

We would like to thank Cancer registry of Research Center of Gastroenterology and Liver Diseases staffs for their valuable collaboration in this study.

References

1. Boyle P, Langman J S. ABC of colorectal cancer: Epidemiology. *BMJ*. 2000; 321:805-808
2. James AS, Campbell MK, Hudson MA. Perceived barriers and benefits to colon cancer screening among African Americans in North Carolina: how does perception relate to screening behavior? *Cancer Epidemiol Biomarkers Prev*. 2002; 11: 529-534.
3. Stone WL, Krishnan K, Campbell SE, Qui M, Whaley SG, Yang H. Tocopherols and the treatment of colon cancer. *Ann NY Acad Sci*. 2004; 1031: 223-233.
4. Islamic Republic of Iran, Ministry of Health and Medical Education, Office of Deputy , Center for Diseases Control, Cancer office. *Iranian Annual National Cancer Registration Report 2005-2006*. March 2007.
5. Mosavi-Jarrahi A, Zali MR, Mohagheghi M.A. Changes in GI Cancer Incidence Iran: last 25 years. *Institute cancer central*. 2005.
6. Esna-Ashari F, Sohrabi MR, Abadi AR, Mehrabian AA, Mofid B, Bohluli M, Akbari ME. Colorectal Cancer Prevalence According to Survival Data in Iran. *Iranian J Cancer Prevention*. 2009; 2 (1): 15-18.
7. Chu KC, Tarone RE, Chow WH, et al. Temporal patterns in colorectal cancer incidence, survival, and mortality from 1950 through 1990. *J Natl Cancer Inst* .1994; 86:997-1006.
8. Devesa SS, Blot WJ, Stone BJ, et al. Recent cancer trends in the United States. *J Natl Cancer Inst* .1995; 87:175-182.
9. Blomqvist P, Ekblom A, Nyren O, Krusemo U, Bergstrom R, Adami H.O. Survival After Colon Cancer 1973-1990 in Sweden. *Annals of Surgery*. 1997; 225(2):208-16.
10. Soleyman A, Kaya S, Izmirli M, Tuncer I, Doğan E, Ozbek H, Sayarlioglu H. Analysis of survival factors in patients with advanced-stage gastric adenocarcinoma. *Med Sci Monit*. 2006; 12(5): 221-229.
11. Kaplan E, Meier P. Non parametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457–81.
12. Cox DR. Regression model and life tables. *J R Stat Soc*. 1972;(B)34:187–220.
13. Hosseini S.V, Izadpanah A, Yarmohammadi H. epidemiological changes in colorectal cancer in Shiraz, Iran: 1980-2000. *ANZ J. Surg*. 2004; 74: 547–549.
14. Takahashi K, Mori T, Yasuno M. Histologic grade of metastatic lymph node and prognosis of rectal cancer. *Dis Colon Rectum*. 2000; 43: S40-6.
15. Ogata Y, Torigoe S, Matono K, Sasatomi T, Ishibashi N, Shida S, et al. Prognostic factors after potentially curative resection in stage II or III colon cancer. *Kurume Med J*. 2005; 52(3):67-71.
16. Liang JL, Wan DS, Pan ZZ, Zhou ZW, Chen G, Li LR, et al. Multivariate regression analysis of recurrence following curative surgery for colorectal cancer. *Ai Zheng*. 2004; 23(5):564-7.
17. Xu FY, Di MJ, Dong JK, Wang FJ, Jin YS, Zhu YM, Lai MD. Influence of clinical and pathomorphological parameters on prognosis in colon carcinoma and rectal carcinoma. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2006 ;35(3):303-10.
18. Compton CC, Fielding LP, Burgart LJ, Conley B, Cooper HS, Hamilton SR, et al. Prognostic factors in colorectal cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med*. 2000 ;124(7):979-94.
19. Kenneth S. H. Chok J, Wai Lun Law. Prognostic Factors Affecting Survival and Recurrence of Patients with pT1 and pT2 Colorectal Cancer. *World J Surg*. 2007; 31:1485–1490
20. Nilsson KR, Berenholtz SM, Dorman T, Garrett P, Kaufman HS, Pronovost PJ. Preoperative predictors of blood transfusion in colorectal cancer surgery. *J Gastrointest Surg*. 2002; 6: 753-762.
21. Han Liang, Xiao-Na Wang, Bao-Gui Wang, Yuan Pan, Ning Liu, Dian-Chang Wang, Prognostic factors of young patients with colon cancer after surgery. *World J Gastroenterol*. 2006 ; 12(9):1458-1462
22. Xu FY, Di MJ, Dong JK, Wang FJ, Jin YS, Zhu YM, Lai MD. Influence of clinical and pathomorphological parameters on prognosis in colon carcinoma and rectal

carcinoma. *Zhejiang Da Xue Xue Bao Yi Xue Ban*. 2006; 35(3):303-10.

23. Jagoditsch M, Lisborg PH, Jatzko GR, Wette V, Kropfisch G, Denk H, et al. Long-term prognosis for colon cancer related to consistent radical surgery: multivariate analysis of clinical, surgical, and pathologic variables. *World J Surg*. 2000; 24(10):1264-70.

24. He WJ, Wang L, Hu H, Kang SY, Qian HX, Xu FM. Correlation of invasion, metastasis, and prognosis in low and middle rectal cancer. *Ai Zheng*. 2002; 21(11):1222-5.

25. Enderlin F, Gloor F. Colorectal cancer: the relationship of staging to survival. A cancer registry study of 800 cases in St. Gallen-Appenzell. *Soz Praventivmed*. 1986; 31(2): 85-8.

26. Wood CB, Gillis CR, Hole D, Malcolm AJ, Blumgart LH. Local tumor invasion as a prognostic factor in colorectal cancer. *Br J Surg* 1981; 68(5):326-8.

27. Oya M, Takahashi S, Okuyama T, Yamaguchi M, Ueda Y. Synchronous colorectal carcinoma: clinico-pathological features and prognosis. *Jpn J Clin Oncol* 2003; 33 (1) :38-43.