

## RESEARCH ARTICLE

# Applying Additive Hazards Models for Analyzing Survival in Patients with Colorectal Cancer in Fars Province, Southern Iran

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### Abstract

**Introduction:** Colorectal cancer (CRC) is a commonly fatal cancer that ranks as third worldwide and third and the fifth in Iranian women and men, respectively. There are several methods for analyzing time to event data. Additive hazards regression models take priority over the popular Cox proportional hazards model if the absolute hazard (risk) change instead of hazard ratio is of primary concern, or a proportionality assumption is not made. **Methods:** This study used data gathered from medical records of 561 colorectal cancer patients who were admitted to Namazi Hospital, Shiraz, Iran, during 2005 to 2010 and followed until December 2015. The nonparametric Aalen's additive hazards model, semiparametric Lin and Ying's additive hazards model and Cox proportional hazards model were applied for data analysis. The proportionality assumption for the Cox model was evaluated with a test based on the Schoenfeld residuals and for test goodness of fit in additive models, Cox-Snell residual plots were used. Analyses were performed with SAS 9.2 and R3.2 software. **Results:** The median follow-up time was 49 months. The five-year survival rate and the mean survival time after cancer diagnosis were 59.6% and 68.1±1.4 months, respectively. Multivariate analyses using Lin and Ying's additive model and the Cox proportional model indicated that the age of diagnosis, site of tumor, stage, and proportion of positive lymph nodes, lymphovascular invasion and type of treatment were factors affecting survival of the CRC patients. **Conclusion:** Additive models are suitable alternatives to the Cox proportionality model if there is interest in evaluation of absolute hazard change, or no proportionality assumption is made.

**Keywords:** Colorectal neoplasms- survival analysis- proportional hazards models- additive models

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### Introduction

Cancer ranks as the second and the third cause of death in developing countries and in Iran respectively (Mousavi et al., 2009). Colorectal cancer (CRC) (also called colon or bowel cancer) is one of the gastrointestinal cancer types invading the tissues of the colon. CRC is the most common fatal cancer and ranks as the third cause of death worldwide and the third and the fifth in Iranian women and men respectively (Zare-Bandamiri et al., 2016). Studies reveal that the incidence of colorectal cancer is hereditary only in 20% patients and the other 80% patients are affected by several modifiable factors including, physical inactivity, obesity and overweight, high consumption of red meat, and smoking (Naccarati et al., 2007). Correction of each one of these risk factors has a significant impact on the occurrence of the disease;

for example, recent investigations have shown that doing regular physical activities at a desirable level can reduce the risk of colorectal cancer by 20% (Larsson and Wolk, 2007). Studies, also, indicates that 5-year survival rate of colorectal cancer in Iran is less than 50% which is lower than that of the other Asian and European countries with 70% and 60%, respectively. This is due to a variation in the onset of disease screening in Iran and other countries, that is, the counties which proceeded with disease screening have higher levels of survival rates of patients because of primary diagnosis. Colorectal cancer screening in Iran started by the Ministry of Health and Medical Education in 2012 (Ghahremani et al., 2016).

Survival analysis is a set of different statistical methods used to study the risk factors associated with the incidence of clinical events. Regression models for survival data are Cox proportional hazards models, accelerated failure

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time models and additive hazards models (Klein and Moeschberger, 2005). The Cox proportional hazards models and Additive hazards models examine various factors affecting the risk of disease, but the accelerated failure time models are used to investigate the impact of various factors on the duration of defeat stage (Hougaard, 2012).

An essential and restrictive assumption in popular Cox proportional hazards models is the proportionality of the risk for all the variables studied. If the assumption is not made, an alternative will be the well-known but less often used method, additive hazards model. Unlike the proportional hazards model which estimates hazard ratios, an additive model estimates the difference in hazards: the absolute difference in the instantaneous failure rate per unit of change in the exposure variable. Based on the estimate of difference in hazards, one can further estimate the change in cumulative incidence: when the cumulative hazard is small (e.g., rare events), the change in cumulative hazard approximates the difference in risk of disease due to exposure, that is, the attributable risk due to exposure (excess risk). Therefore, when the attributable risk is of primary interest or the proportional hazard assumption is violated, an additive hazard regression model may be more appropriate (Xie et al., 2013).

Sometimes the effect of an independent variable on survival rate might vary over time. Nonparametric Additive hazards model provides plots to evaluate the effect of this variable and analyze its trends over time (Huffer and McKeague, 1991; Hougaard, 2012). In general, Additive hazards model are a non or semiparametric methods which provide a better fit for survival data (Hougaard, 2012). Previous research studies have used the common models such as Cox proportional hazards models, Kaplan Meier, Log Rank test and etc. to examine the factors affecting survival of patients with colorectal cancer (O'Connell et al., 2004; Group, 2009; Van Cutsem et al., 2011; Chan et al., 2016; Mlecnik et al., 2016; Zare-Bandamiri et al., 2016). The Additive hazard models are used only in a limited number of recent studies (Hosmer and Royston, 2002; Ghahremani et al., 2016).

## Materials and Methods

The data used in this study gathered from the studying of the medical records of 561 colorectal cancer patients who were admitted to Namazi Hospital, Shiraz, Iran, during the 2005 to 2010 years and followed until December 2015. By reviewing medical records the status of each patient was determined. Also, to find out the final status of the patients that their status were censored telephone interviews were used. 12 variables consisted of diagnosis age, patients gender, tumor site, tumor stage, T-stage (Based on the American Joint Committee on Cancer classification), tumor differentiation level, tumor size, type of treatment (neoadjuvant versus adjuvant systemic treatment), lymphovascular, perineural invasion, number of dissected lymph nodes and positive lymph nodes (N-stage) were used for modelling.

## Statistical Analysis

In this study, we used the additive hazards models consisted of Aalen's additive hazards model, Lin and Ying's additive hazards model and the proportional hazards model.

### Cox Proportional Hazards Model

Currently, the most popular regression model for survival analysis is the cox proportional hazards model. Based on this model, the relation between failure times and p-dimensional vector of independent variables (X) has the form

$$(1) \lambda_i(t) = \lambda_0(t) \exp(\gamma_1 X_{i1} + \dots + \gamma_p X_{ip})$$

where  $\lambda_0(t)$  is the baseline hazard function and  $\gamma_i$ ,  $i=1, \dots, p$  is unknown time-independent coefficients. The crucial assumption of proportional hazards in the Cox model means that the proportional effect of a treatment dose not vary with time (David, 1972).

### Lin and Ying's additive hazards model

In this semiparametric additive hazards model the constant effects of covariates upon baseline hazard is additive. According to this model, hazard function for failure time (Ti) has following relation with p-dimensional vector X (covariates).

$$(2) \lambda_i(t) = \lambda_0(t) + \gamma_1 x_{i1}(t) + \dots + \gamma_p x_{ip}(t)$$

where  $\lambda_0(t)$  is baseline hazard function. Coefficients  $\gamma_i$ ,  $i=1, \dots, p$  are time independent additive effects (Lin and Ying, 1995).

### Aalen's Additive Hazards Model

In this non-parametric model the effects of covariates (constant or variable effect) upon baseline hazard is additive. According to this model, the relation between hazard function and failure time (Ti) with p-dimensional vector X (covariates) takes the form

$$(3) \lambda_i(t) = \lambda_0(t) + \gamma_1(t) x_{i1}(t) + \dots + \gamma_p(t) x_{ip}(t)$$

where  $\lambda_0(t)$  is baseline hazard function. Coefficients  $\gamma_i$ ,  $i=1, \dots, p$  are time dependent additive effects. The Aalen's model provides cumulative regression function plots (Aalen's plot) that display how the effects of covariates change over the time. In the other words, Aalen's plot shows time-dependent or constant effect of each covariate (Aalen, 1989). In this model, tests such as Kolmogorov-Smirnov test and Cramer Von Mises test have been presented for evaluating time invariant effect (Martinussen and Scheike, 2007).

All of the statistical analysis performed using SAS 9.2 and R 3.2. The p value less than 0.05 was statistically significant.

## Results

More than half of the subjects were male (57.6%). Mean age of diagnosis was  $55.74 \pm 13.67$  years (range:

Table 1. The Demographic Characteristics of the Colorectal Cancer Patient

Variables	Mean ± SD
Age	55.74 ± 13.67
Number of dissected lymph nodes	8.97 ± 7.94
Number of positive lymph nodes	1.42 ± 3.26
Tumor Size	4.83 ± 1.90
Sex	Number (%)
Male	323 (57.6 %)
Female	238 (42.4%)
Site of tumor	
Rectum	283(50.4%)
Right and Transverse colon	109 (19.8%)
Left colon	52 (9.3%)
Sigmoid	117 (20.9%)
T-stage	
T1	7 (1.2%)
T2	111 (19.8%)
T3	424 (75.6%)
T4	19 (3.4%)
N-stage	
N0	339 (60.4%)
N1	120 (21.4%)
N2	76 (13.5%)
Unknown	26(4.2%)
Stage	
I	96 (17.1%)
II	247 (44%)
III	181 (32.3%)
IV	23 (4.1%)
Unknown	14(2.5%)
Grade	
Well differentiated	371 (66.1%)
Moderately differentiated	155 (27.6%)
Poorly differentiated	34 (6.1%)
Unknown	1(0.2%)
Lymphovascular invasive	
Yes	200 (35.7%)
No	354(63.1%)
Unknown	7(1.2%)
Perineural invasive	
Yes	160 (28.5%)
No	395 (70.4%)
Unknown	6 (1.1%)
Treatment Method	
Adjuvant therapy	455 (81.1%)
Neoadjuvant therapy	106 (18.9%)
Hospital	
Governmental	243 (43.3%)
Non-governmental	318 (56.7%)

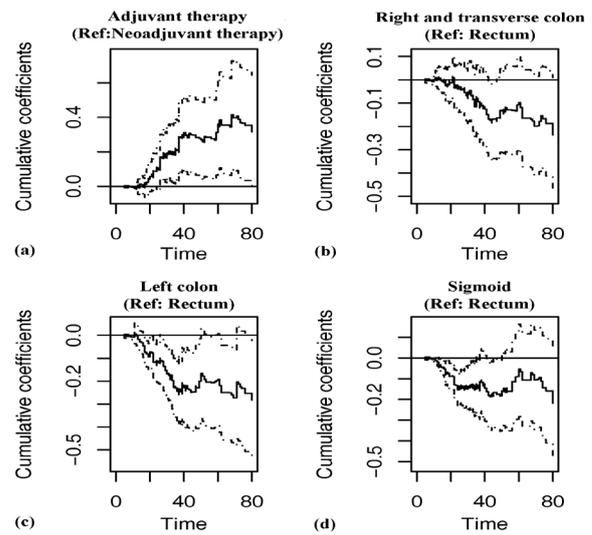


Figure 1. Estimate of Cumulative Excess Risk of Treatment (a) and site of tumor (b, c, d) with A 95% pointwise confidence interval based on Aalen's additive model

18-88 years). Of all the patients, 181(49%) had tumor size greater than 5 cm, 283(50.4%) had rectum cancer site, 204(36.4%) diagnosed with advanced stages (stages III&IV) and 455(81.1%) were treated with adjuvant therapy (table1). Finally, from 561 patients, 221 died (39.4%). The median follow-up time was 49 months. The five-year survival rate and the mean survival time after cancer diagnosis were 59.6% and 68.12±1.4 months respectively.

Univariate analysis showed that variables such as age of diagnosis, primary site of tumor, T-stage, N-stage, stage, tumor differentiation level(grade), proportion of involved lymph nodes, lymphovascular, perineural invasion and type of treatment were prognostic factors for the survival of the CRC patients and the other clinic pathological characteristics were not statistically significant (results not

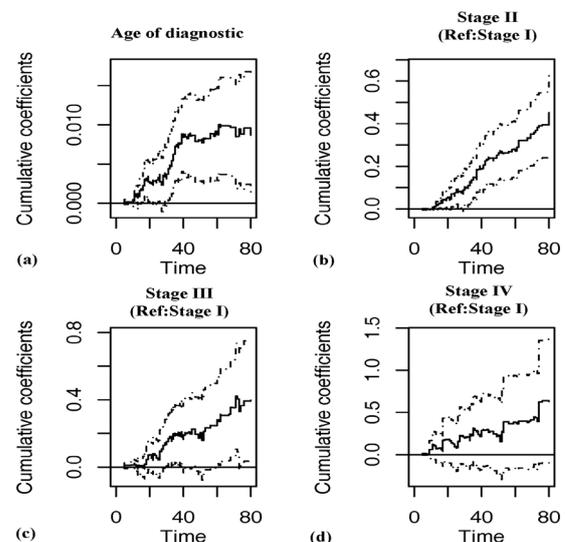


Figure 2. Estimate of Cumulative Excess Risk of Age of Diagnostic (a) and stage (b, c, d) with a 95% pointwise confidence interval based on Aalen's additive model

Table 2. Multivariate Analysis of Prognostic Factors Based on Lin and Ying’s Additive Hazards Model and Cox Model

Variables	Lin and Ying’s model		Cox model	
	Coefficient (se)	p	HR (95%CI)	P
Age of diagnosis	0.0001 (0.0000)	0.003	1.02 (1.01-1.03)	0.001
Site of tumor				
Rectum (reference)	---	---	1	
Right and transverse colon	-0.0026 (0.0016)	0.106	0.69 (0.47-1.03)	0.06
Left colon	-0.0043 (0.0017)	0.011	0.51 (0.28-0.91)	0.02
Sigmoid	-0.0029 (0.0016)	0.073	0.70 (0.49-1.01)	0.06
Stage				
I (reference)	---	---	1	
II	0.0055 (0.0011)	<0.0001	4.41 (2.12-9.16)	<0.001
III	0.0055 (0.0021)	0.0053	4.70 (2.14-10.34)	<0.001
IV	0.0086 (0.0047)	0.0625	6.19 (2.38-16.10)	<0.001
Grade				
Well differentiated	---	---	1	
Moderately differentiated	0.0017 (0.001)	0.2655	1.14 (0.88-1.57)	0.28
Poorly differentiated	0.0027 (0.003)	0.3676	1.35 (0.77-2.36)	0.41
Proportion of positive Lymph nodes	0.0049 (0.0027)	0.0686	1.87 (0.98-3.58)	0.06
Lymphovascular invasive				
No (reference)	---	---	1	
Yes	0.0056 (0.0019)	0.004	1.79 (1.26-2.55)	0.001
Perineural invasive				
No (reference)	---	---	1	
Yes	0.0009 (0.0021)	0.6675	1.07 (0.74-1.54)	0.73
Treatment				
Adjuvant therapy( reference)	---	---	1	
Neoadjuvant therapy	0.0057 (0.0021)	0.0066	1.73 (1.22-2.45)	0.002

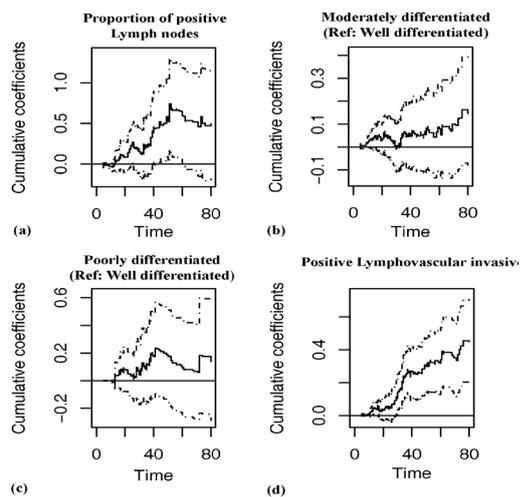


Figure 3. Estimate of Cumulative Excess Risk of Proportion of Positive Lymph Nodes (a), grade (b, c) and Lymphovascular invasive (d) with a 95% pointwise confidence interval based on Aalen’s additive model

shown here). Then, variables with a P-value less than 0.2 were entered the multivariate Cox proportional hazards model. Since the tumor stage is based on N-stage and T-stage, just tumor stage was included in multivariate model to avoid multicollinearity. The Cox proportional

hazards model considered age of diagnosis, site of tumor, stage, proportion of positive lymph nodes, lymph vascular invasion and type of treatment as factors affecting the hazard of death due to CRC as shown in table 2. In order to approve the proportional hazards assumption, a test based on correlation between the Schoenfeld residuals and ranked survival times was done. According to this test, proportionality assumption was confirmed for all covariates and factors ( $p > 0.05$ ) except site of tumor ( $p = 0.04$  for sigmoid site).

Since the proportionality hazard assumption was not made for the site of tumor, and, on the other hand, we wanted to assess the attributable risk, instead of the risk ratio, additive hazards regression models were used. At first, a Lin and Ying’s additive model with time invariant coefficients fitted to the data. The results of Lin and Ying’s additive hazards model are given in table 2. For better fitting, centered age (centering on its mean) and exponential of proportion of positive lymph nodes were included in the model. The model showed that the age of diagnosis, site of tumor, stage, proportion of positive lymph nodes, lymph vascular invasion and type of treatment as factors affecting the hazard of death due to CRC. While the result of the Lin and Ying’s additive model was similar to the Cox proportional hazards model in detecting the prognostic factors, they had completely

different interpretation. For example, in Cox proportional hazards model the exponential of coefficient of type of treatment was 1.73, showing the hazard for patients with neoadjuvant therapy was 1.73 times of hazard for patients with adjuvant therapy. In contrast, the coefficient in Lin and Ying's additive model was 0.006 that meant patients with neoadjuvant therapy had an increase in hazard of 0.006 in comparison to patients with adjuvant therapy (Table 2).

To analyze the data by nonparametric Aalen's additive model, the same covariates in Cox model and Lin and Ying's additive model were used here. To illustrate the results, the cumulative regression functions versus time were plotted in which dots show 95% confidence intervals. To assess time invariant effect, both the Kolmogorov-Smirnov test and Cramer Von Mises test were used. Based on Kolmogorov-Smirnov test only the proportion of positive lymph had time-varying effect ( $p=0.02$ ), but on Cramer Von Mises test none of the variables had time-varying effect. Figure 1(a) showed the estimate of cumulative excess risk for type of treatment (adjuvant therapy compared to neoadjuvant therapy) and a 95% point-wise confidence interval. In this Figure, the estimated cumulative regression coefficient increased nearly linearly over the time of the study. This showed that neoadjuvant therapy increased the hazard compared to adjuvant therapy during the study, so it did not have time varying effect. In addition, the slope of this plot illustrated the excess mortality due to using adjuvant therapy compared to neoadjuvant therapy. Moreover, since the zero line was not within 95 percent confidence interval, the effect of type of treatment was significant. Consequently, the Figures 1(b), 1(c) and 1(d) respectively showed the estimate of cumulative excess risk of right and transverse colon, left colon and sigmoid compared to the rectum. The Figures displayed that tumors in rectum increased the hazard in comparison with the left colon, but the difference was not significant for other sites of tumor.

Based on Figure 2(a), there is an increase in the hazard rate with increasing age that remains in effect over the entire time. In addition, the steeper slope before 40 months suggested that age of diagnosis had an early effect. The plot for stage II was nearly linear with a positive slope over the study, suggesting that the effect of the stage II did not change over the time of studying and increased the hazard over the entire time of the period (Figure 2(b)). Although the Figures for stage III and stage IV were similar to stage II in trend, the zero line was within the lower 95 percent confidence band in stage IV, suggesting that it was not significant compared to stage I probably because of low percent of patients with stage IV: 4% (Figure 2(c), 2(d)). The trend of cumulative coefficient for proportion of positive lymph nodes and a 95% point-wise confidence interval was nearly linear with a slight positive slope over the first 50 months, but it was steady after this time. This showed that proportion of positive lymph nodes had an early effect (Figure 3(a)). The lymphovascular invasion had a positive effect during the time; therefore, the positive Lymphovascular invasion increased the hazard over the entire time of the period (Figure 3(b)). For the effect of grade, in Figures 3(c) and 3(d) the zero line was contained

within 95 percent confidence interval, illustrating no significant effect. The estimated cumulative regression coefficient for perineural invasion was constant over the time and the zero line was contained within 95 percent confidence interval (the plots not shown here).

Based on the Cox-Snell residual plots the estimated cumulative hazard curves approximately follow the 45-degree lines, so the additive hazard models fit the data well.

## Discussion

The mean survival time for colorectal cancer patients in this study was 68.12 months and the five year survival rate was reported to be 59.6% that is similar to some studies (Luo et al., 2013; Zare-Bandamiri et al., 2016). Although this five year survival rate was greater than some other studies worldwide (Moradi et al., 2009; Al-Ahwal et al., 2013).

In this study, the age at diagnosis time had significant effect on the survival of CRC patients in both univariate and multivariate models, which is similar to other studies (Zare-Bandamiri et al., 2016). Based on Aalen model, the age at diagnosis effect was not dependent on the time and there was an increase in the hazard rate with increasing age at diagnosis that remained in effect over the entire time of the period, but the effect was more in early duration of the follow-up. In another study it was indicated that age at diagnosis had no effect on survival rate (Akhoond et al., 2010). Some other studies which investigated age effect (not age at diagnosis) showed significant relationship (Henry et al., 2009; Moradi et al., 2009; Ghahremani et al., 2016).

Among other studies in Iran, the relationship between age at diagnosis and survival of colorectal wasn't significant (Henry et al., 2009; Ghanbari et al., 2012; Mehrabani and Almasi-Hashiani, 2012). Our results suggested that the size of tumor was not a significant factor, being similar to some studies and contrary to others (Moghimi-Dehkordi et al., 2008; Zare-Bandamiri et al., 2016).

Sex, in our study, was not significant which is consistent with other studies (Akhoond et al., 2010; Luo et al., 2013), however, women had less hazard of death due to colorectal cancer. There was a relationship between sex and survival time in other studies in Iran (Asghari-Jafarabadi et al., 2010; Ghanbari et al., 2012; Mehrabani and Almasi-Hashiani, 2012). Also, the studies done in other countries proved the sex effect (Elsaleh et al., 2000; Henry et al., 2009; Al-Ahwal et al., 2013).

Patients with left colon tumor had less hazard than those with rectum tumor so that the attributable risk for left colon was -0.0043, that is, patients with left colon had decreased hazard equal to 0.0043 compared to patients with rectum tumor. Patients with other site tumors had less hazard compared to those with rectum tumor although no significant difference could be seen. A study performed in Iran also reported less hazard for patients with colon in comparison with rectum (Ghahremani et al., 2016). It was considerable that the effect of tumor in left colon compared to rectum was not dependent on the time and

the regression coefficient decreased linearly during the time of the follow-up. These findings were consistent with others that reported significant effect of tumor site on survival time around the world (Elsaleh et al., 2000).

Other important factors for colorectal cancer patients in this study were T-stage and N-stage, so that the more severe stage, the more hazard of death due to CRC. Other researchers also verified that T-stage and N-stage were significant pathologic factors associated with survival time of colorectal cancer patients (Mehrkhani et al., 2009; Silva and Damin, 2013; Parnaby et al., 2015; Chan et al., 2016).

In the additive models, the coefficients for stages II, III and IV were positive that means patients with higher stage had higher hazard; also, the effect of stage did not change over time and increased the hazard over the entire time, so it had an invariant effect. Moreover, excess risk for stage IV (0.0086 based on Lin and Ying's model) was more than other stages, but it was not significant probably because of low percent of patients with stage IV: 4%. In a study patients with stage III had higher risk than patients with stage I & II, although the authors did not use Aalen additive model (Gilard-Pioc et al., 2015). This fact is verified in other studies among Iranian community (Moghimi-Dehkordi et al., 2008; Akhoond et al., 2010; Ghahremani et al., 2016; Zare-Bandamiri et al., 2016). We found that grade of cancerous cell with moderately differentiated increased hazard compared to well differentiated in univariate model. However, in the multivariate model this effect canceled due to the other important prognostic factors. Other studies drew this conclusion on the grade of tumor (Moghimi-Dehkordi et al., 2008; Akhoond et al., 2010; Karimi Zarchi et al., 2011; Parnaby et al., 2015).

Proportion of positive lymph nodes was an important factor on colorectal cancer survival rate in both univariate and multivariate models. This finding was consistent with studies conducted by (30, 31, 35, 36). Moreover, in our study one percent increase in proportion of positive lymph nodes had 0.0049 additional hazard (Le Voyer et al., 2003; Chang et al., 2007; Silva and Damin, 2013; Parnaby et al., 2015).

In our study, lymphovascular invasion compared to non-invasion was a significant factor in both models that was similar to two other studies in Iran (Mehrkhani et al., 2009; Akhoond et al., 2010). The need for criteria in evaluation of lymphovascular invasion was necessary because this assessment may influence patient prognosis and change the way of clinical treatment (Harris et al., 2008). Furthermore, in our study patients with positive lymphovascular invasion had an additional hazard of 0.0056 than negative lymphovascular invasion patients.

Perineural invasion was another factor that had a significant effect on colorectal survival time based only on univariate model. Two meta-analyses indicated that PNI was a poor prognostic factor in CRC patients which was similar to interpretation of ours (Yang et al., 2015; Zhou et al., 2015). In contrast, other study stated that PNI was an independent prognosis factor in survival time of CRC patients (Liebig et al., 2009).

Our study showed that neoadjuvant therapy had more hazard than adjuvant therapy under both univariate and multivariate analysis and the effect of treatment

did not vary over the time. The treatment was found to be an important factor affecting survival time in other studies (Parnaby et al., 2015). Patients hospitalized in governmental hospital compared to non-governmental had no better or worse hazard rate.

The additive models were also applied to survival analysis of other types of cancer (Baldi et al., 2006; Maroufizadeh et al., 2011).

This study applied semiparametric and non-parametric additive models besides Cox proportional hazards model to analyze colorectal cancer patients. The results of Lin and Ying's additive model were similar to Cox proportional hazards model in our data although there was little difference between significant effects of stage IV for additive models compared to Cox proportional hazards model. The interpretation of additive models and Cox proportional hazards model are very different so that the exponential of coefficients in Cox proportional hazards model are relative hazards, but those in additive models are the attributable risks. The results of Aalen's additive model were similar to Lin and Ying's additive model in terms of significant effects. Furthermore, Aalen's additive model revealed the time invariant effect of prognostic factors. So using all of the models covers different aspects of the data. The relative hazards estimated by Cox models can be especially useful in understanding the magnitude of association, which may scientifically be important. This means if the baseline hazard of disease is low, the absolute number of additional cases related to exposure may be small, but the relative risk can still be strong. However, the absolute risk can be especially useful for public health planning and intervention if the actual number of additional cases of a disease is of interest.

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