RESEARCH ARTICLE

XRCC1 Gene Polymorphism, Clinicopathological Characteristics and Stomach Cancer Survival in Thailand

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Abstract

Background: Stomach cancer is one of leading causes of death worldwide. In Thailand, the incidence and mortality of stomach cancer are in the top ten for cancers. Effects of DNA repair gene X-ray repair cross complementary protein 1 (*XRCC1*) polymorphisms and clinicopathological characteristics on survival of stomach cancer in Thailand have not been previously reported. The aim of this study was to investigate the effects of *XRCC1* gene and clinicopathological characteristics on survival of stomach cancer patients in Thailand. Materials and Methods: Data and blood samples were collected from 101 newly diagnosed stomach cancer cases pathologically confirmed and recruited during 2002 to 2006 and followed-up for vital status until 31 October 2012. Genotype analysis was performed using real-time PCR-HRM. The data were analyzed using the Kaplan-Meier method to yield cumulative survival curve, log-rank test to assess statistical difference of survival and Cox proportional hazard models to estimate adjusted hazard ratio. Results: The total followed-up times were 2,070 person-months, and the mortality rate was 4.3 per 100 person-months. The median survival time after diagnosis was 8.07 months. The cumulative 1-, 3-, 5-years survival rates were 40.4%, 15.2 % and 10.1 % respectively. After adjustment, tumour stage were associated with an increased risk of death (p= 0.036). The *XRCC1* Gln339Arg, Arg/Arg homozygote was also associated with increased risk but statistically this was non-significant. Conclusions: In addition to tumour stage, which is an important prognostic factor affecting to the survival of stomach cancer patients, the genetic variant Gln339Arg in *XRCC1* may non-significantly contribute to risk of stomach cancer death among Thai people. Larger studies with different populations are need to verify ours findings.

Keywords: *XRCC1* polymorphism - survival - clinicopathological - stomach cancer - Thailand

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Introduction

More than 990,000 cases of stomach cancer have been diagnosed and more than 738,000 deaths have occurred worldwide. The highest mortality rates were reported in Eastern Asia with a rate of 28.1 per 100,000 in males and 13.0 per 100,000 in females. The lowest mortality rates were reported in the Northern America (Ferlay et al., 2010). In Thailand, stomach cancer is one of the most common forms of malignancies. The overall estimated age-standardized incidence rate (ASR) for males was 4.5 per 100,000 for and 1.4 per 100,000 for females (Suwanrungruang et al., 2006).

The X-ray repair cross-complementing group 1 (*XRCC1*) is one type of genetic variant that has been implicated in cancer susceptibility. From the evidence 297 case-control studies found *XRCC1* Arg399Gln increases risk for overall cancer (Yi et al., 2013) and many studies suggest that the *XRCC1* gene is one of the most important genetic risk factors for stomach cancer (Hong et al., 2009; Engin et al., 2011; Yuan et al., 2011; Chen et., 2012; Pan et al., 2012; Qiao et al., 2013) and previous studies have pointed to *XRCC1* polymorphism as an important prognostic factor for survival of gastric cancer (Shim et al., 2010; Tahara et al., 2011; Deng et al., 2014; Zhang et al., 2014).

In terms of clinicopathological characteristics, Previously studies have reported tumor site, tumor size, lymph node ratio, staging of diseases, lymph node metastasis, tumor invasion, distant of metastases, Borrmann type, depth of invasion and surgical margin status all related to survival of stomach cancer patients (Yin

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et al., 2012; Li et al., 2013; Okholm et al., 2014; Posteraro et al., 2014; Deng et al., 2015). However, few studies have conducted in Thailand and none have been investigated the effects of clinicopathological characteristics or *XRCC1* polymorphism on survival of stomach cancer patients. It is quite possible that genetic and lifestyle differences between Thai and other population (particularly western population). This study investigates the effects of *XRCC1* gene and clinicopathological characteristics on survival of stomach cancer patients in Thailand.

Materials and Methods

Study subjects

In total, 101 newly diagnosis stomach cancer patients were included in this study. All cases were histologically confirmed and diagnosed according to the International Classification of Diseases for Oncology (ICD-O 3rd). Subjects were recruited from Srinagarind Hospital and Khon Kaen Regional Hospital, Khon Kaen Province, Northeast Thailand, during 2002 to 2006. All of patients were followed-up until death or the end of the study (31 October, 2012). Factors of interest were retrieved from medical records including age at diagnosis, gender, site of diseases, surgery type, histological type, histological grading and stage of disease. *XRCC1* genotyping was the performed (described below). The classical endpoint in this study is survival time of stomach cancer. Status of each patient was checked from medical records and by linkage with the death registry of the Thai national statistics database.

Laboratory methods

Specimen collection and DNA extraction: Blood samples were taken from all stomach cancer patients diagnosis in the study period (n=101). Whole blood samples of 3-5 ml were collected and centrifuged at 3,000 rpm for 15 minute to separate plasma, buffy coat and red blood cells. All specimens were stored at -20°C at the cancer unit, Faculty of Medicine, Khon Kaen University. The genomic DNA was extracted from the buffy coat at Nagoya city university medical school, Japan.

PCR amplification and genetic polymorphisms detection

The DNA analyses were performed by using real-time polymerase chain reaction with high resolution melting technique (Real-time PCR-HRM). DNA amplification was performed in a 96-well plate in the light Cycler® 480 Real-Time PCR System. The amplification of *XRCC1* Gln399Arg gene was used two primers, [Forward]: 5´-AGT GGG TGC TGG ACT GTC-3´ and [Reverse]:5´-TTG CCC AGC ACA GGA TAA-3´. The HRM data were analyzed using the light Cycler® 480 Gene Scanning software version 1.5(Roche) and was performed at Department of Microbiology, Faculty of Medicine, Khon Kaen University.

Statistical analysis

Survival times of patient were calculated for each patient and were started from the date of diagnosis until the date of death or the end of follow-up (31 October, 2012). Percentages were used to describe categorical data and means with standard deviations or medians with ranges were used to describe continuous data. The observed survival rate was calculated and summarized using Kaplan-meier survival curves. The statistics used to compare survival between groups was performed by using the log-rank test. The univariate and multivariate Cox proportional hazard regression models were used to estimate the association between explanatory variable and survival experience, presented crude hazard ratios (HR) and adjusted HRs and their 95% confidence interval (CI). All analysis was conducted using the SAS statistical package (version 9.3; SAS institute, Cary, NC) and significance level of 0.05 was used for all analysis.

The Ethics Consideration

The study was approved by the Khon Kaen University Ethics Committee for Human Research. The reference number is HE561259.

Results

Demographic characteristics of stomach cancer

The results of the descriptive analysis were summarized in Table 1. Of the 101 patients with stomach cancer, 57 (56.4%) were males. The mean age was 52.7 years. Most of the cancer patients were married 78.2 %, had only a primary school education were 74.3% and farmers or agricultural worker were 69.3%. Table 2 shows the frequencies and the contribution of pathological characteristics of cases. The most commonly specified anatomical sites of stomach cancer were the antrum (45.6% of all cases) and the cardia (16.8% of all cases). The most common type of surgery was subtotal gastrectomy (49.5%). Regarding histopathology, the most frequently specified histological type of malignancy was signet ring cells carcinoma (24.7% of all cases), and in most patients histological grade was assessed as poorly differentiated (58.4%) or unable to be assessed (28.8%). Stage IV cancers (53.5%) preponderated the majority of the patients. The allele frequencies of *XRCC1* Gln399Arg polymorphisms for Gln/Gln, Gln/Arg and Arg/Arg genotypes were 47.5%, 40.6% and 11.9 %, respectively.

Survival rate of stomach cancer

The total follow-up person time was 2,070 person-months, and the overall mortality rate was 4.3 per 100 person-months (95%CI: 3.49 to 5.35). Table 3 presents the survival rates. The cumulative 3-, 6- and 9 months, 1-, 3- and 5-years survival rates were 86.9 %, 63.7 % , 46.5% 40.4 %, 15.2 % and 10.1 %, respectively. The median survival time of stomach cancer after diagnosis was 8.07 months (95%CI: 6.00 to 10.23; Figure 1). The Figures 2-5 presented survival times of stage of diseases, histology type, histology grading and *XRCC1* polymorphisms. The median survival time of Stage IB, Stage II, Stage IIIA, Stage IIIB, Stage IV and Unknown stage were 9.10, 41.80, 22.90, 14.14, 8.67, 6.27 months respectively. Regarding to *XRCC1* polymorphisms, the median survival time of Arg/Arg, Gln/Arg and Gln/Gln genotype were 15.60, 12.30 and 7.33 months respectively.

Table 1. The General Characteristics of Stomach Cancer

Variables	Nunber(101)	%
Gender		
Male	57	56.4
Female	44	43.6
Age (years)		
<60	70	69.3
> 60	31	30.7
Mean + - SD	52.7 (+ - 11.42)	
Median (Min:Max)	53 (28:70)	
Marital status		
Single	6	5.9
Married	79	78.2
Separated, widowed	16	15.9
Occupation		
Agriculture, farmer	70	69.3
Office, technical work	18	17.8
Professional work	13	12.9
Education		
Illiteracy	2	2
Primary school	75	74.3
Secondary school or higher	24	23.7

Table 2. Frequencies and Distribution of Pathological Characteristics of Stomach Cancer

Variables	Nunber(101)	%
Site of diseases		
Fundus	1	1.0
Pylorus	2	2.0
Body	7	6.9
Cardia	17	16.8
Antrum	46	45.6
Stomach, Not otherwise specified	28	27.2
Type of surgery		
Gastric mucosa biopsy	21	21.0
Subtotal gastrectomy	50	49.5
Near totalgastrectomy	7	6.9
Total gastrectomy	15	14.5
Orther	8	8.1
Histology type		
Tubular adenocarcinoma	1	1.0
Diffuse type	5	5.0
Signet ring cell carcinoma	25	24.7
Adenocarcinoma, Not otherwise specified	69	69.3
Histology Grading		
Well differentiated	10	9.9
Moderately differentiated	11	10.9
Poorly differentiated	59	58.4
Grade can't be assessed	21	28.8
Stage of diseases		
Stage IB	3	3.0
Stage II	5	5.0
Stage IIIA	9	8.9
Stage IIIB	6	5.9
Stage IV	54	53.5
Unknown Stage	24	23.8
XRCC1 G339A genotype		
Gln/Gln	48	47.5
Gln/Arg	41	40.6
Arg/Arg	12	11.9

Other = Gastrojejunectomy, Hemi gastrectomy and Esophagogastrectomy

The associated of Clinicopathological and XRCC1 gene Polymorphisms with survival of stomach cancer

Table 4 shows after adjusting for lymph node metastasis, comorbidity and complication. Tumour stage IV and Unknown stage lead to increased risked of death (HR: 3.6; 95%CI: 1.35 to 9.43; HR: 3.0; 95%CI: 1.08

Table 3. Survival Rate of Stomach Cancer After Diagnosis

Survival time	Median time (Months)	95% CI	Survival rate (%)	95% CI
3 Months	1.9	0.63-2.07	86.9	78.49-92.17
6 Months	3.5	2.80-4.60	63.7	53.36-72.27
9 months	5.1	4.00-5.70	46.5	36.43-55.90
1 Year	5.5	4.40- 6.07	40.4	30.73-49.87
3 Years	6.9	5.70-8.73	15.2	8.93-22.90
5 Years	7.8	5.80-10.23	10.1	5.17-16.97

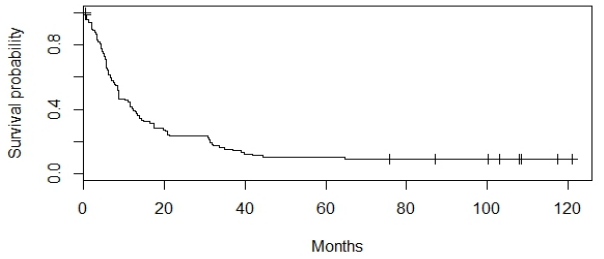

Figure 1. Overall Survival Curve of Stomach Cancer

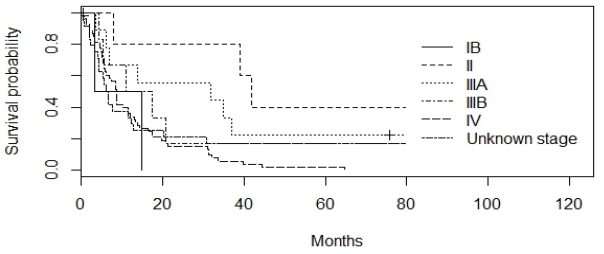

Figure 2. Survival Curve of Stomach Cancer by Stage of Diseases

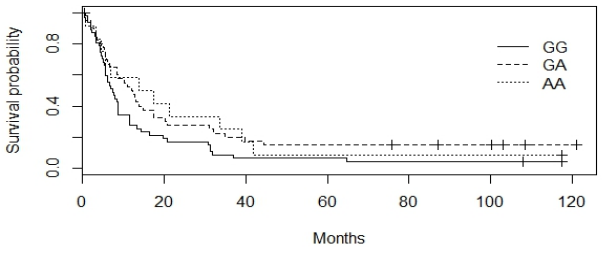

Figure 3. Survival Curve of Stomach Cancer by *XRCC1* Gene

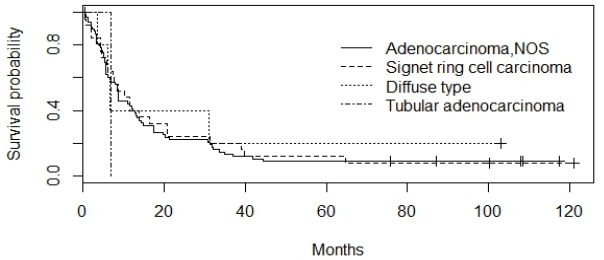

Figure 4. Survival Curve of Stomach Cancer by Histology Type

Table 4. Pathological and *XRCC1* Gene as Effected to Survival of Stomach Cancer (Multivariate Analysis)

Variable	Number(%)	Median time (Months) 95% CI	Crude HR (95% CI)	Adjusted HR (95% CI)	p-value
Gender					0.306
Male	57(56.4)	10.3(6.1-14.3)	1	1	
Female	44(43.6)	8.1(5.7-12.3)	1.2 (0.81-1.87)	1.2 (0.81-1.89)	
Age					0.414
<60	70(69.3)	8.6(6.7-12.3)	1	1	
> 60	31(30.7)	10.1(4.8-17.4)	0.9(0.62-1.49)	1.0 (0.59-1.44)	
Site of diseases					0.308
Fundus, Pylorus, Body	10(10.4)	13.7(5.1-20.2)	1	1	
Cardia	17(16.8)	12.8(3.4-20.2)	2.2 (0.87-5.65)	2.3 (0.90-6.08)	
Antrum	46(45.6)	7.8(5.6-11.9)	2.0 (0.86-4.81)	2.1 (0.85-5.04)	
Stomach, NOS	28(27.2)	8.4(5.5-12.3)	2.1 (0.89-5.31)	2.4 (0.95-6.02)	
Type of surgery					0.149
Gastric mucosa biopsy	21(21.0)	6.5(2.3-12.3)	1	1	
Subtotal gastrectomy	50(49.5)	11.6(6.1-17.3)	0.4 (0.05-2.65)	0.3 (0.04-3.05)	
Near totalgastrectomy	7(6.9)	11.9(2.8-64.6)	0.3 (0.03-2.47)	0.2 (0.02-2.10)	
Total gastrectomy	15(14.5)	11.5(1.9-31.4)	0.3 (0.04-2.45)	0.3 (0.04-2.73)	
Orther	8(8.1)	4.5(1.2-7.8)	1.2 (0.14-9.45)	1.3 (0.15-11.85)	
Histology type					
Tubular adenocarcinoma, Diffuse type	6(6.0)	6.7(3.5-NA)	1	1	0.657
Signet ring cell carcinoma	25(24.7)	10.2(5.8-20.6)	0.6 (0.08-4.60)	0.7 (0.08-5.54)	
Adenocarcinoma, NOS	69(69.3)	8.7(5.7-12.9)	0.7 (0.09-4.72)	0.9 (0.11-6.81)	
Histology grading					0.638
Well differentiated	10(9.9)	6.8(2.3-31.4)	1	1	
Moderately differentiated	11(10.9)	12.8(5.7-21.3)	0.8 (0.45-1.63)	0.7 (0.27-1.88)	
Poorly differentiated	59(58.4)	8.7(6.7-13.0)	1.3 (0.77-1.79)	0.8 (0.37-1.70)	
Grade can't be assessed	21(28.8)	6.1(3.5-14.8)	0.8 (0.46-1.37)	0.6 (0.25-1.54)	
Stage of diseases					0.036
Stage IB+II	8(7.9)	39.1(3.4-NA)	1	1	
Stage IIIA+IIIB	15(14.8)	15.6(5.4-35.1)	1.4 (0.49-4.15)	1.9 (0.63-5.71)	
Stage IV	54(53.5)	8.7(5.8-11.5)	2.8 (1.09-7.02)	3.6 (1.35-9.43)	
Unknown Stage	24(23.8)	6.2(4.0-12.3)	2.3 (1.87 - 6.21)	3.0 (1.08-8.34)	
XRCC1 G339A genotype					0.136
Gln/Gln	48(47.5)	7.3(5.5-8.7)	1	1	
Gln/Arg	41(40.6)	12.3(6.5-17.5)	0.6 (0.40- 0.98)	1.0 (0.52-2.02)	
Arg/Arg	12(11.9)	15.6(3.3-39.1)	1.6 (1.02- 2.50)	1.8 (0.89-3.45)	

*Stomach cancer; 95% CI, 95% confidence interval, were adjusted for complication, comorbidity and metastasis using Cox proportional hazard regression models, p-value from Partial likelihood ratio test; NA, Not Applicable; NOS, not otherwise specified, Other = Gastrojejunectomy, Hemi gastrectomy and Esophagogastrectomy

Table 5. Final Multivariate Model of Significant Factors Independently Associated with Hazard of Death

Variable	HRa	95% CI	p-value
Stage IV	1.7	1.09-2.59	0.019

*Stomach cancer; HRa, Adjusted Hazard Ratio; 95% CI, 95% confidence interval p-value base on stepwise cox proportional hazards regression

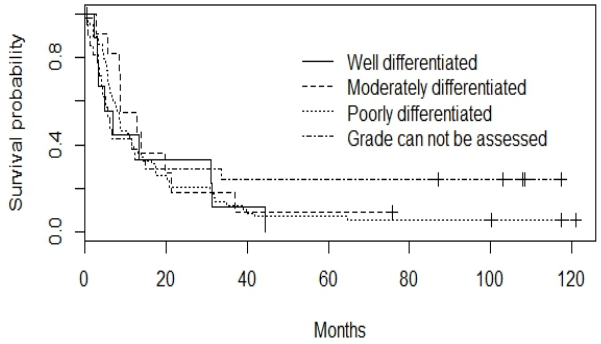

Figure 5. Survival Curve of Stomach Cancer by Histology Grading

to 8.34). The Polymorphisms of *XRCC1* Gln339Arg were associated increased risked of death with Arg/Arg homozygote but we can't demonstrated statistically significant. Table 5 show the final multivariate model of significant factors independently associated with hazard of death base on stepwise Cox proportional hazards regression and found a tumour stage IV was associated with hazard of death 1.7-fold (95%CI: 1.09 to 2.59).

Discussion

Our study investigated the factors associated with mortality among stomach cancer patients. This is firstly reported on the effected of the *XRCC1* gene and clinicopathological characteristics on the survival of stomach cancer patients among Thai peoples. Our resulted found the stage of diseases was the factors affected to survival of patients, which is consistent with previous studies have been reported. They found out that the staging of diseases were impotent factors affected to survival of gastric cancer patients especially advance stage of diseases (Choi et al., 2011; Kwon et al., 2014).

The study on the effected of the *XRCC1* gene to survival of stomach cancer patients, many studies have been explored much on the associated of *XRCC1* gene and clinical outcome to survival of patients under treatment by chemotherapy (Liu et al., 2007; Wang et al., 2012; Zou and Yang, 2012; Xu et al., 2014) but non studies have been conducted in Thailand. Our results have found out that the *XRCC1* Gln399Arg, Arg/Arg homozygote was affected to survival of stomach cancer patients but statistically non significant.

The tumor location and type of surgeries has important factors affected to survival of stomach cancer patients. Ours study found the tumor location and type of surgeries were not increases risked of death. This is inconsistent with preciously studies done in Korea, France and China they found out that the location of cancer in the stomach and type of surgeries were important factor that effected to survival of stomach cancer patients (Choi et al., 2011; Deng et al., 2014; Son et al., 2014; Herbreteau et al., 2015). The histology grading and histology type, our study found not increases risked of death, Similar findings have been previously reported elsewhere (Kwon et al., 2014; Son et al., 2014).

In conclusion, our study suggests the stage of diseases is the factors affecting to survival of stomach cancer in Thai population. We did not find any effects of *XRCC1*polymorphisms, tumor location, surgeries type, histology grading and histology type were associated with an increase risk of death of stomach cancer patients. It would be necessary to confirm these findings in the larger sample size.

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