RESEARCH COMMUNICATION

Depression and Survival in Chinese Patients with Gastric Cancer: A Prospective Study

Hui Yu[1&], Yaoxian Wang[2,3&], Xin Ge[4], Xiaoke Wu[3*], Xiaoqin Mao[5]

Abstract

Aim: Depression is thought to be a predictor of poor survival among cancer patients. In our study, we aimed to investigate the association between depression and survival in patients with gastric cancer. **Methods**: The subjects were a total of 300 patients aged 20-75 years who had histological confirmed diagnosis of gastric cancer from January 2004 to May 2006. Three months after patients diagnosis, depression was scored using by the Depression Status Inventory (DSI) designed by Willian WK Zung. The follow-up period consisted of a total of 13,643 person-months. A Cox's regression analysis was used to assess the association between depression and survival. **Results**: The percentage of subjects with depression according to the DSI depression criteria was 31%. Tumor stage and treatment methods were significantly associated with depression of patients. Age (60 years or older), annual income, tumor stage, lymph nodes metastasis and treatment were significantly associated with increased hazard ratio (HR) for gastric cancer survival. The adjusted HR for mortality risk in gastric cancer patients with depression tended to be high (HR=3.34, 95% CI=1.23-5.49) and a significant trend was found (P<0.05). **Conclusion**: The data obtained in this prospective study in Chinese support the hypothesis that depression is associated with poor survival among gastric cancer patients. Further studies with a large sample and longer term follow-up period are needed.

Keywords: Depression - survival - gastric cancer - Chinese population

Introduction

About one million new cases of stomach cancer were estimated to have occurred in 2008 (988,000 cases, 7.8% of the total), making it currently the fourth most common malignancy in the world, behind cancers of the lung, breast and colo-rectum. More than 70% of cases (713,000 cases) occur in developing countries (467,000 in men, 246,000 in women), and half the world total occurs in Eastern Asia (mainly in China) (IARC, 2011). In China, gastric cancer is the third cause of death from the most common cancer, with an age-standardized incidence of 21.1 and 15.2 cases per 100,000 person-years for men and women, respectively, according to the 2008 national cancer statistics (Yang, 2006). Depression is the most common psychiatric disorder among patients with cancer. It is well known and documented that cancer patients are likely to have depressive symptoms after a diagnosis of cancer or during the clinical course of cancer (Ford et al., 1995; Aass et al., 1997). The prevalence of psychiatric disorders in cancer patients varies greatly among studies ranging from 9%-60% (Montazeri et al., 1998; Costantin et al., 1999). Because of such an association, depression has been considered to have an impact not only on the progression, but also on the initiation, of cancer (Dunlop et al., 2004; Mossey and Gallagher, 2004). There have been several prospective studies in which the relationship between depression and cancer prognosis was observed; however, results have remained inconclusive (Nakaya et al., 2006; Lehmann et al., 2011).

Certain methodological limitations may have contributed to the conflicting results. First, the time-lag between the time of psychological investigation and the outcome followed-up of cancer patients could have affected the results. It is often difficult to confirm whether a stress assessment actually preceded the sever prognosis of cancer, because the mechanism of deceasing the survival of cancer patients. Second, whether a single psychological assessment, as is used in most studies can reflect long-term psychological state is unknown. Third, studies on genetic examination relevant to cancer progress at the time of psychological assessment is very limited. Previous study investigated stress-related genetic changes and have found that stress was associated with poor DNA repair in X-irradiated lymphocytes of high-distress psychiatric inpatients (Kiecolt-Glaser et al., 1985), the suppression

[1]Cardiopulmonary Function Room, [2]Department of Gynecology, Third Affiliated Hospital of Harbin Medical University, [3]Department of Gynecology, First Affiliated Hospital of Heilongjiang University of Chinese Medcine, [4]Department of General Surgery, Heilongjiang Province Hospital, Harbin, [5]Department of Digestion Medicine, First People's Hospital of Yunnan Province, Kunming, China &Equal Contributions * For Correspondence: maoxiaoqin555@yahoo.cn

of synthesis of a DNA repair enzyme, methyltransferase, in rats (Glaser et al., 1985). Therefore, to further examine the association between depression and survival in patients with gastric cancer, we conducted a prospective cohort study in Chinese. This study assessed depression using a structured clinical interview at 3 months after diagnosis, and focused on survival of patients with gastric cancer.

Materials and Methods

We invited patients with gastric cancer who were scheduled for treatment from January 2004 to May 2006. The study included 334 patients aged 20-75 years who had histological confirmed diagnosis of gastric cancer from January 2004 to May 2006. An interview based prospective study was carried out to measure anxiety and depression in patients with gastric cancer. The intention was to interview all gastric cancer cancer inpatients attending our hospital. 34 patients refused to interview due to their physical or psychological condition, and the participation rate was 89.8%. A psychologist in a face-to-face interview administered the questionnaire after the patients diagnosed after three months. Data on demographic characteristics and clinical information including age, gender, educational status, TNM stage, lymph nodes metastasis, cancer site and time since diagnosis were extracted from case records. Depression was scored using by the Depression Status Inventory (DSI) designed by Willian WK Zung (Wang, 1999; Xiao, 1999). The DSI is a 20 items, self-reported questionnaire that measures the presence and severity of depressive symptoms using a self-rating scale from 1 to 4 (0 being least depressed and 4 being the most depressed). The scale has been previously validated in Hospital in Fujian Province of China. Scores for each question were summed, calculating a final DSI score. The total score of DIS was 80. The degree of depression was measured by DSI score/80. Depression degree were classified into four groups: No depression (<0.5), light depression (0.50-0.59), moderate depression (0.60-0.69) and heavy depression (>0.70) (Wang, 1999).

Survival was determined from the time of biopsy proven diagnosis, and the end point for survival analysis was cancer-specific death. Patients were followed up at their clinic or information on date and cause of death was checked with that received by the cancer registration. The person-months of follow-up were counted for each subject from the date of study enrollment until the date of death or the end of the study period (May, 2011). The follow-up period consisted of a total of 13643 person-months (median=46.5 Months, range=3.7-64 months). A total of two subjects were lost to follow up during the study period. 105 deaths from all causes were identified.

We used the Statistical Package for the Social Sciences (SPSS) version 12.0 (SPSS Inc., Chicago, IL, USA) for the data analysis. We analyzed the unadjusted [hazard ratio (HR)] of survival in patients with surgically treated gastric cancer according to various demographic and medical variables. A univariant Cox's regression analysis was used to assess the association between depression and survival. The relative risk [hazard ratio (HR)] and 95% CI were calculated from the Cox regression model

Table 1. Demographic and Medical Characteristics of Study Subjects According to Depression

Characteristics	Depression status		χ^2	P-value
	Absence(%) N=207	Presence(%) N=93		
Sex				
Male	128(62)	50(54)	1.73	0.19
Female	79(38)	43(46)		
Age (years)				
<45	31(15)	16(17)	0.78	0.68
45-60	108(52)	51(55)		
>60	68(33)	26(28)		
Education level (years)				
<6	83(40)	30(32)	2.61	0.27
6~9	48(23)	22(24)		
>9	77(37)	44(41)		
Annual income (RMB)				
<5000	41(20)	25(27)	3.12	0.21
5000-10000	60(29)	30(32)		
>10000	106(51)	38(41)		
Tumor type				
Intestinal carcinomas	120(58)	52(56)	0.11	0.74
Diffuse carcinomas	87(42)	41(44)		
Tumor site				
Upper part	56(27)	20(21)	4.81	0.18
Middle part	41(20)	22(24)		
Lower part	77(37)	28(30)		
Whole part	33(16)	23(25)		
Tumor stage				
I	48(23)	9(10)	17.84	<0.001
II	52(25)	12(13)		
III	39(19)	25(27)		
IV	68(33)	47(50)		
Lymph nodes metastasis				
No	81(39)	33(35)	0.36	0.55
Yes	126(61)	60(65)		
Treatment				
Operable	120(58)	41(45)	4.61	0.03
Inoperable	87(42)	51(55)		

for all significant predictors from cancer diagnosis to the endpoint of the study (event). All statistical tests were two sided, and differences were taken as significant when the P value was less than 0.05.

Results

We first compared the characteristics of subjects according to the DSI depression criteria using χ^2 analysis to compare two categorical variables. The percentage of subjects with depression according to the DSI depression criteria was 31%. Subjects with depression were more likely to have a poor tumor stage (p<0.001) (Table 1). The subjects took inoperable treatment were more likely to have depression. The other demographic and medical variables were not associated with depression.

In the univariate Cox proportional hazard regression analysis, six demographic or clinical variables-age (60 Years or older), annual income, tumor stage, lymph nodes metastasis and treatment were significantly associated with increased HR for gastric cancer survival compared with each referent category. Therefore, the multivariate analysis used these variables to evaluate their effect on survival (Table 2).

Table 2. Unadjusted Hazard Ratios (HR) for Death from all Causes Among Patients with Gastric Cancer

Characteristics	Median survival (months)	HR(95% CI)	P-value
Sex			
Male	45.1	1.0(reference)	-
Female	46.2	0.82(0.59-1.40)	0.45
Age (years)			
<45	49.5	1.0(reference)	-
45-60	46.7	1.5(0.95-2.21)	0.06
>60	40.7	2.7(1.32-4.09)	<0.001
Education level (years)			
<6	46.5	1.0(reference)	-
6~9	47.2	1.31(0.84-1.6.0)	0.09
>9	45.9	1.53(0.96-1.97)	0.06
Annual income (RMB)			
<5000	43.2	1.0(reference)	-
5000-10000	44.9	0.82(0.78-1.32)	0.14
>10000	48.7	0.65(0.41-0.93)	<0.05
Tumor type			
Intestinal carcinomas	46.2	1.0(reference)	-
Diffuse carcinomas	46.9	0.98(0.92-1.18)	0.54
Tumor site			
Upper part	46.7	1.0(reference)	-
Middle part	47.8	0.92(0.83-1.37)	0.43
Lower part	45.8	1.13(0.94-1.34)	0.37
Whole part	44.3	1.63(0.97-2.15)	0.07
Tumor stage			
I	57.8	1.0(reference)	-
II	50.4	1.86(1.15-3.07)	<0.05
III	45.6	2.45(1.56-3.96)	<0.001
IV	39.2	4.43(2.01-5.30)	<0.001
Lymph nodes metastasis			
No	56.2	1.0(reference)	-
Yes	42.1	3.52(1.79-4.73)	<0.001
Treatment			
Operable	47.8	1.0(reference)	-
Inoperable	44.1	1.81(1.15-2.84)	<0.05

Table 3. Kaplan-Meier Survival Estimation of Median Survival and HRs with Gene Polymorphism

Depression status	n(%)	Median Survival (in month)	HR (95% CI)[1]	HR (95% CI)[2]
No depression	207(69)	47.7	1.0(Reference)	1.0(Reference)
Light depression	32(10.7)	47.1	1.13(0.98-1.94)	1.15(0.99-2.01)
Moderate depression	41(13.7)	44.5	1.59(1.09-2.84)	1.85(1.32-3.35)
Heavy depression	20(6.7)	40.3	3.03(1.17-7.76)	3.41(1.24-7.94)

[1]Unadjusted; [2]Adjusted for age, sex, education level, annual income, tumor site, stage, lymph nodes metastasis and treatment

Table 3 showed the gastric cancer survival according to the depression diagnosis as assessed by the DSI depression criteria. The HR for mortality risk in gastric cancer patients with highest depression tended to be high but the trend was not significant: the unadjusted HR was 3.03 (95% CI=1.17-7.76) (p=0.29), compared with patients without depression. After controlling for age, sex, education level, annual income, tumor site, stage, lymph nodes metastasis and treatment, the effect of depression on survival was basically unchanged, and the multivariable HR of survival for individuals in the highest level of depression was 3.41 (95% CI=1.24-7.94), compared with individuals without depression. A significant trend was found in adjusted HR (trend for p=0.031) (Table 3).

Discussion

The data obtained in the present prospective cohort study in Chinese support the hypothesis that depression is associated with survival among gastric patients. Our study had several methodology advantages compared with previous studies on depression and survival in patients with cancer. Firstly, we assessed depression using a structured face to face interview. Secondly, we considered the potential confounding variables like education level, annual income, tumor stage and etc.

In our analysis, we examined whether physical states and lifestyle characteristics influenced the association between depression and cancer survival. Lifestyle characteristics and lymph nodes metastasis were significantly associated with survival in patients with gastric cancer but were not associated with depression. We observed small differences in the point estimates of the HR depending on whether multivariate adjustments were made for lifestyle characteristics and tumor situation (Table 2), but the a trend of HR after adjusting the potential factors. Thus, these factors probably had interaction with the trend between depression and cancer survival seen in this study. However, most of patients in our study were with early stage cancer, and the physical burden and medical cost burden on the patients was thought to be smaller than that for patients with advanced cancer. The interaction of depression, physical burden and medical cost burden and cancer survival should be examined among patients with advanced cancer in the future.

For previous studies examining the association between depression and cancer survival, several prognostic factors has been hypothesized to play a role in the possible association between depression and survival from cancer. Potential intermediaries include endocrinological or immunological pathways (Oken et al., 1982; Maunsell et al., 1995; Okano et al., 2001; Nordin et al., 2001). Our findings suggest that the depression in the gastric cancer patients might play an important role in survival.

To date, two prospective studies regarding the association between depression and survival in patients with gastric cancer have been reported (Chen et al., 2011; Wu et al., 2011). Wu et al. followed 231 patients with gastric cancer stage 1 to IV for 6 months. Depression was assessed after treatment, significant difference was found (Wu et al., 2011). Chen et al. found subjects with higher depression scores had an poor survival compared with the subjects with lower scores (p<0.05) (Chen et al., 2011). Our finding did not show the tumor stage is significantly associated with depression, the reason might be the small sample size.

Our study has several limitations. Firstly, the number of subjects and deaths were relatively small (300 patients and 105 deaths). Although a significant association was found between psychological depression and survival in the gastric cancer patients, the analysis may have not sufficient statistical power to detect associations between lifestyle factors and tumor situation with depression, thus further analysis involving large sample is needed. Second, 34 patients refused to participate because of the psychological or physical burden, or other reasons. The

analyzed subjects may have had a better health status, with regard to psychological or physical burden, than the initial patient group, and the present results might underestimate the association between psychological variables and survival in patients with gastric cancer. Thirdly, we focused on depression only at 3 months after diagnosis, but the depression might be changed after a long interval after diagnosis and can be confounded by life events other than the situation of gastric cancer. Therefore, further study should focused on the depression after long-term follow-up.

In conclusion, the data obtained in this prospective study in Chinese support the hypothesis that depression is associated with survival among gastric cancer patients. Further studies with a larger sample and longer term follow-up period are needed.

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