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Original Article

A retrospective study of the clinical differences of Uygur breast cancer patients compared to Han breast cancer patients in the Xinjiang region of China

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Abstract: Background: Studies support biological disparities of breast cancer among races/ethnicities. Uygur is a minority ethnic group in China with a genetic admixture of Caucasian and East Asian. The Han ethnic group makes up the majority of the Chinese population. We aim to study and compare the clinical differences and survival rate in these two ethnic groups in order to improve prophylaxis. Methods: A retrospective analysis of the medical records of 264 Uygur and 287 Han breast cancer patients including demographic data, clinical and pathological parameters, TNM status, Ki-67 and treatment information was collected. The patients were followed up at three month intervals for 2 years then every 6 months for 3 to 4 years postoperatively. Chi-square tests were performed to compare characteristics, and a log-rank test was used for ranked data. Overall survival and disease free survival were analyzed by Kaplan Meier tests. Results: Uygur was statistically different in terms of: marital status; occupation; body mass index; duration of breast feeding; period of complaint; pathological composition; size of primary tumor; number of metastatic and resected lymph nodes; pathological staging; expression of nm23; chemotherapy and radiotherapy. The 5-year overall survival rate of Uygur breast cancer patients was 89.2% compared to 91.7% in Han (P = 0.129). The disease free survival of Uygur breast cancer patients was 79.3% compared to 84.5% in Han (P = 0.040). Conclusion: The different characteristics of Uygur breast cancer patients compared to Han breast cancer patients and their lower survival rates indicate that management strategies should be implemented to improve patient outcome.

Keywords: Breast neoplasms, survival, ethnic groups, China, population characteristics

Introduction

Breast cancer (BC) has become the most prevalent malignancy in Chinese females, due to the incidence rate of the disease in China that is increasing more rapidly than in other countries [1, 2]. The incidences of BC in large cities such as Beijing and Shanghai are reaching levels similar to that of the countries with the highest prevalence in the world [3]. The region of Xinjiang is no exception, with an increasing trend of BC occurring in both the Uygur and Han populations of Chinese women each year.

As a region located in the middle of Asia and on the Silk Road that used to extend from Rome to China, the region of Xinjiang played an important role in the merging of East and West civilizations. The province of Uygur therefore developed as an admixture of the anthropological features of both Europeans and Asians [4, 5], with a majority population higher than that of Han in the Xinjiang region.

An example of the way racial differences influence BC is in African American women, who have a lower incidence compared to white American women but a higher overall mortality [6]. The causes and genetic mechanisms of racial/ethnic disparities in terms of the incidence of BC remain unknown [7]. Whilst currently there is a lack of available authorized sta-

Table 1. Comparison of the general data between the Han group (n = 287) and Uygur group (n = 264) of BC patients

variables	Han (n (%))	Uygur (n (%))	X^2 (df)	*P*-value
Age (years)			7.25 (3)	0.064
≤ 35	41 (14.3)	55 (20.8)		
36-45	101 (35.2)	103 (39)		
46-55	86 (30)	61 (23.1)		
> 55	59 (20.6)	45 (17)		
Marital status			12.615 (1)	< 0.001
single	4 (1.4)	20 (7.6)		
married	283 (98.6)	244 (92.4)		
Degree of education			3.707 (2)	0.157
elementary or low	120 (41.8)	121 (45.8)		
middle/high school	109 (38)	80 (30.3)		
junior college or above	58 (20.2)	63 (23.9)		
Occupation			43.718 (4)	< 0.001
worker	64 (22.3)	48 (18.2)		
administrative staff	57 (19.9)	40 (15.2)		
teacher	13 (4.5)	25 (9.5)		
farmer	22 (7.7)	69 (26.1)		
freelance work	131 (45.6)	82 (31.1)		
Complication of CCVD or DM*			0.582 (1)	0.446
yes	55 (19.2)	44 (16.7)		
no	232 (80.8)	220 (83.3)		
Body Mass Index			29.135 (2)	< 0.001
≤ 23.9	158 (55.1)	93 (35.2)		
24-27.9	93 (32.4)	97 (36.7)		
≥ 28	36 (12.5)	74 (28)		
Family history of cancer			0.348 (1)	0.555
yes	59 (20.6)	49 (18.6)		
no	228 (79.4)	215 (81.4)		

Abbreviations: BC-breast cancer; CCVD-cardiocerebral vascular disease; DM-diabetes mellitus.

tistics, the incidence of BC in the Uygur population is lower than the Han population, In contrast, mortality due to BC is higher in Uygur BC patients compared to Han BC patients. The Uygur genetic characteristics have been investigated. Xu et al. [8] found that Uygurs from northern and southern Xinjiang share 47% and 52% of their ancestry with Europeans respectively, with 53% and 48% of their ancestry from East Asia respectively. Genetic and socioeconomic factors play important roles in emphasizing racial differences [9-11], both of which are areas of interest for many researchers. Aside from genetic differences, the typical eating and living characteristics of Uygur citizens differs greatly to those of Han citizens. For example Uygur citizens generally consume a high animal fat diet, have higher birth rates and subsequent longer breast feeding times, a higher divorce rate, and a higher body mass index (BMI), as previously reported [12, 13].

Few studies have investigated systemically and wholly, the clinical differences of Uygur BC patients in comparison to Han BC patients. The aim of this study was investigate these differences and the survival in these two groups. This information should help reveal how the outcome of these Chinese can be improved by managing disease treatment and prevention.

Methods

Patients

The medical records of Uygur and Han BC patients admitted to the Affiliated Tumor Hospital of Xinjiang Medical University from February 2005 to September 2009 were retrospectively analyzed. Only operable BC patients with integrated clinical data were chosen. The selected patients ideally received integrated therapy. The inclusion criteria were patients who were firstly diagnosed with invasive breast cancer then (1) invasive breast cancer was confirmed by the pathology, (2) in accordance with operation indications (3) had complete pathologic results, (4) had complete medical records, (5) the preoperative Karnofsky performance scores (KPS) were greater than 85 points. The exclusion criteria was (1) patients preoperatively treated with radiation therapy and chemotherapy or endocrine therapy, (2) whose tumor were resected in other hospitals, (3) carcinoma in situ, (4) rare cases, (5) male breast cancer, (6) familial breast cancer, (7) another kind of malignancy prior to or simultaneously with the diagnosis of

Table 2. Comparison of the menstruation and fertility status between the Han group (n = 287) and Uygur group (n = 264) of BC patients

Variables	Han (n (%))	Uygur (n (%))	X^2 (df)/Z	*p*-value
Menarche (age in years)			1.721*	0.085
≤ 12	33 (11.5)	20 (7.6)		
13	61 (21.3)	40 (15.2)		
14	72 (25.1)	75 (28.4)		
15	52 (18.1)	64 (24.2)		
≥ 16	69 (24)	65 (24.6)		
Menopause status			1.663 (1)	0.197
no	200 (69.7)	197 (74.6)		
yes	87 (30.3)	67 (25.4)		
Live birth number			8.099*	< 0.001
0	12 (4.2)	10 (3.8)		
1	157 (54.7)	44 (16.7)		
2	59 (20.6)	100 (37.9)		
≥ 3	59 (20.6)	110 (41.7)		
Abortion number			1.895*	0.058
0	101 (35.2)	132 (50)		
1	95 (33.1)	47 (17.8)		
2	62 (21.6)	50 (18.9)		
≥ 3	29 (10.1)	35 (13.3)		
Age at first parturition (year)			20.043 (1)	< 0.001
≤ 25	151 (54.9)	187 (73.6)		
> 25	124 (45.1)	67 (26.4)		
Duration of breast feeding (month)			4.907*	< 0.001
0	33 (12)	8 (3.1)		
1-11	90 (32.7)	57 (22.4)		
≥ 12	152 (55.3)	189 (74.4)		

*The results of the "z" test; Abbreviation: BC-breast cancer.

BC. Finally, 287 cases of Han BC patients and 264 Uygur BC patients were included.

Data collection and interpretation of variables

Data were collected retrospectively from the electronic medical record (EMR)/computer-based patient record (CPR). This included demographic data, clinical and pathologic parameters, TNM status, Ki-67 and treatment information.

Freelance work indicates individuals that decide to either work, or not work, without the restriction of others, for example self-employed individuals or stay at home mothers. The family history of cancer represents individuals who have a first degree relative with any form of malignancy.

The protein expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), nuclear specific Ki-67 and metastasis-associated nm23 was analyzed by immunohistochemistry (IHC). Only negative and positive results were obtained due to technical restrictions and the methodologies used at the time.

The interpretation of the staining of the molecular subtypes included: "Luminal A" represented ER (+), PR (+) or HER-2 (-) IHC staining; "Luminal B" represented ER (+), PR (+) or HER-2 (+) IHC staining; "Her-2 overexpression" represented ER (-), PR (-) or HER-2 (+) IHC staining and "triple negative" represented ER (-), PR (-) or HER-2 (-) IHC staining as previously described [14].

In terms of chemotherapytreatment,"unique" indicated one form of combined chemotherapy whilst "changed" indicated a switch to another form of chemotherapy treatment.

Postoperative follow-up

Patients were followed up at 3 month intervals during the first 2 years, then every 6 months until 3-4 years postoperatively. The routine postoperative examination included a physical examination, blood tests with tumor related antigen levels, B-mode ultrasound, mammography, computed tomography (CT) and magnetic resonance imaging (MRI) for the presence of metastasis or recurrence. All patients were followed up to death or March 2013. The patients were then followed up by telephone conversation. The nearest reexamination records were recorded in the computer system if patients were not able to be contacted by telephone. More than 95% of the patients were successfully followed up.

Table 3. Comparison of pain complaints between the Han group (n = 287) and Uygur group (n = 264) of BC patients

Variables	Han (n (%))	Uygur (n (%))	X^2 (df)/Z	*P*-value
Complaints			1.197 (2)	0.550
tumor	267 (93)	242 (91.7)		
tumor with pain	11 (3.8)	9 (3.4)		
other symptoms	9 (3.1)	13 (4.9)		
Duration of complaint (month)			1.974*	0.048
≤ 3	204 (71.1)	165 (62.5)		
4-12	58 (20.2)	74 (28)		
> 12	25 (8.7)	25 (9.5)		
Position			0.008 (1)	0.931
left	137 (47.7)	127 (48.1)		
right	150 (52.3)	137 (51.9)		
Location			5.559 (4)	0.235
upper inner quadrant	44 (15.3)	43 (16.3)		
lower inner quadrant	33 (11.5)	32 (12.1)		
upper outer quadrant	130 (45.3)	107 (40.5)		
lower outer quadrant	42 (14.6)	56 (21.2)		
Areola area	38 (13.2)	26 (9.8)		

*The result of the "z" test; Abbreviation: BC-breast cancer.

Disease free survival (DFS) indicates the duration from operation to the time of the following events: recurrence of cancer; primary cancer of heterolateral breast or other sites of the body; a reason for death other than BC or the last follow-up date. Overall survival (OS) indicates the duration from surgery to either tumor related death or the last follow-up date.

Statistical methods

All statistical analyses were conducted using SPSS 17.0 (SPSS Inc., USA). The chi-square test was initially used to compare the percentages of characteristics between different nationalities. A Log-rank test was used for ranked data and the Kaplan Meier test used to compare and evaluate overall survival rate (OS) and disease free survival (DFS). A *P* value of $P \leq 0.05$ was considered statistically significant,

Results and discussion

Results

Of the 908 patients who met the inclusion criteria, 357 were excluded according to the exclusion criteria. Finally 551 patients were included in this study. This was divided according to the two ethnic groups as 264 Uygur and 287 Han. The mean age of the groups were Han 47.34 ± 9.994 and Uygur: 45.27 ± 10.059. As presented in **Table 1**, significant differences were observed between the Uygur and Han BC patients in terms of marital status, occupation and BMI ($p < 0.01$). The Uygur group of BC patients consisted of more single women, farmers, less freelance workers, and more obese patients compared to the Han group of BC patients ($p < 0.01$). There was no significant difference in the remaining variables such as age, the degree of education, complications of cardiovascular disease (CCVD) and diabetes mellitus (DM) and family history of cancer. The menstruation and fertility status of both Uygur and Han BC patients are shown in **Table 2**. There were no significant differences in terms of menarche, menopause status and abortion number between the two groups. In contrast, there were significant differences in variables such as live birth number, first birth before 25 years of age and breastfeeding for longer than 1 year ($P < 0.01$).

There were no significant differences in terms of the location of pain. Only the duration of pain was significantly different between Uygur and Han BC patients ($P = 0.048$), explaining why Uygur BC patients present to doctors later than Han BC patients (**Table 3**).

The pathological data of the present study indicate that statistical differences exist between Uygur and Han BC patients in the variables of: pathological composition ($P = 0.010$); tumor size ($P < 0.01$); the number of metastatic and resected lymph nodes (LN) ($P < 0.01$); pathological stage ($P < 0.01$) and the expression of nm23 protein ($P < 0.001$) (**Table 4**). The cases of exclusive invasive BC, particularly invasive lobular carcinoma and medullary carcinoma was higher in the Uygur group of BC patients compared to the Han group of BC patients ($P = 0.013$). The Han group of BC patients consisted of more patients with multiple compositions,

Table 4. Comparison of the pathological results between the Han (n = 287) and Uygur group (n = 264) of BC patients

Variables	Han (n (%))	Uygur (n (%))	X^2 (df)/Z	*P*-value
Pathological composition			6.665	0.010
Single	212 (73.9)	219 (83)		
IDC	203 (95.8)	193 (88.1)	8.76	0.013
ILC	5 (2.4)	11 (5)		
MC	4 (1.9)	15 (6.8)		
Multiple	75 (26.1)	45 (17)		
IDC + ILC	30 (40)	24 (53.3)	4.238	0.516
IDC + tubular adenocarcinoma	12 (16)	3 (6.7)		
IDC + medullary carcinoma	6 (8)	4 (8.9)		
IDC + myxoadenocarcinoma	4 (5.3)	3 (6.7)		
IDC + apocrine carcinoma	9 (12)	6 (13.3)		
IDC + CIS	14 (18.7)	5 (11.1)		
Tumor size			18.746	< 0.001
T1	128 (44.6)	74 (28)		
T2	145 (50.5)	167 (63.3)		
T3	10 (3.5)	20 (7.6)		
T4	4 (1.4)	3 (1.1)		
Metastatic LN			4.275*	< 0.001
0	153 (55)	92 (36.4)		
1~3	54 (19.4)	68 (26.9)		
4~9	42 (15.1)	43 (17)		
≥ 10	29 (10.4)	50 (19.8)		
Resected LN			4.669*	< 0.001
1~9	36 (12.9)	10 (4)		
10~19	203 (73)	176 (69.6)		
≥ 20	39 (14)	67 (26.5)		
Pathological Staging			21.462	< 0.001
I	84 (29.3)	38 (14.4)		
II	125 (43.6)	118 (44.7)		
III	78 (27.2)	108 (40.9)		
Molecular subtypes			2.527	0.47
Luminal A	179 (62.4)	151 (57.2)		
Luminal B	31 (10.8)	34 (12.9)		
Her-2 positive	27 (9.4)	22 (8.3)		
Tripple negative	50 (17.4)	57 (21.6)		
Ki-67			0.916	0.339
-	81 (28.2)	65 (24.6)		
+	206 (71.8)	199 (75.4)		
Her-2			0.084	0.772
-	229 (79.8)	208 (78.8)		
+	58 (20.2)	56 (21.2)		
Nm23			14.532	< 0.001
-	74 (25.8)	34 (12.9)		
+	213 (74.2)	230 (87.1)		

*The results for the "z" test; Abbreviations: BC-breast cancer; IDC-invasive ductal carcinoma; ILC-invasive lobular carcinoma; MC-medullary carcinoma; CIS- carcinoma in situ; LN-lymph node.

which complicated prognosis. No significant differences were found in multiple compositions between the Uygur and Han groups of BC patients (P = 0.516). Whilst the number of metastatic lymph nodes (LN) corresponded with the number of resected LN, pathological staging of metastatic LN was significantly different between the Uygur and Han groups of BC patients (P < 0.001). There were more positive metastatic LN in the Uygur BC patients, indicating a higher number of stage III BC patients in the Uygur group compared to the Han group of BC patients. The expression of nm23 in Uygur BC patients was higher than that in the Han group of BC patients (87.1%, versus 74.2% P < 0.001). No significant differences were found in the variables of molecular subtypes and the protein expression of Ki-67 and Her-2.

Table 5 indicates that apart from surgery and chemotherapy, other variables such as chemotherapy regiments, chemotherapy cycle number and radiotherapy significantly differed between the two groups, primarily in terms of differing pathologic results. Whilst the Uygur group of BC patients received less breast conserving operations compared to the Han group of BC patients (12.5% versus 8.7% respectively), the difference was not significant. Uygur BC pa-

Table 5. Comparison of the treatment between the Han (n = 287) and Uygur group (n = 264) of BC patients

Variables	Han (n (%))	Uygur (n (%))	X^2 (df)	*P*-value
Operation			2.111 (1)	0.146
breast conserving operation	36 (12.5)	23 (8.7)		
mastectomy	251 (87.5)	241 (91.3)		
Method of chemotherapy			0.878 (1)	0.349
unique	260 (90.6)	245 (92.8)		
changed	27 (9.4)	19 (7.2)		
Chemotherapy regimens			19.628 (3)	< 0.001
methotrexate-based	16 (5.6)	39 (14.8)		
anthracycline-based	112 (39)	89 (33.7)		
vinorelbine-based	71 (24.7)	41 (15.5)		
taxane-based	88 (30.7)	95 (36)		
Number of cycle			6.508 (1)	0.011
≤ 4	33 (11.5)	51 (19.3)		
≥ 5	254 (88.5)	213 (80.7)		
radiotherapy			9.502 (1)	0.009
yes	100 (34.8)	125 (47.3)		
no	187 (65.2)	139 (52.7)		

Abbreviation: BC breast cancer.

tients received significantly more methotrexate and taxane-based chemotherapy (P < 0.01), more chemotherapy cycles of less than 4 (P = 0.011), and more patients underwent radiotherapy (P = 0.009).

The 5-year OS was 91.7% in the Han BC patients and 89.2% in the Uygur BC patients. The OS of Uygur BC patients was lower than that of Han BC patients as reported in the survival curve (**Figure 1A**). This difference between the two groups of BC patients in terms of OS, was not significant (P = 0.129). In contrast, the DFS rate of patients was significantly different between the 2 groups of BC patients (P = 0.040) (**Figure 1B**).

Discussion

The aim of this study was to determine the differences in clinical characteristics and survival between Uygur BC patients and Han BC patients of the Xinjiang region. We have shown in our results that there are many differences between the two groups. Using this information may assist with improving BC patient outcome.

From the results of the present study it is clear that the general characteristics of Uygur BC patients differ from Han BC patients including: a higher divorce rate; more farmers and less freelance workers; a higher BMI; longer breast feeding time; a longer period of complaint; more exclusive pathological composition; larger primary tumor size, more incidences of metastatic carcinoma and resected lymph nodes; later pathological staging; a higher expression of nm23 and lower OS and DFS rates. Among these variables, longer breast feeding time, exclusive pathological composition and higher expression of nm23 protein were the protecting factors in the Uygur BC patients, compared to previously reported prognostic factors of BC [15, 16].

The religious status of Uygurs [17] significantly influences marriage status and reproductive habits. Uygurs are traditionally of Islamic faith. In general, Uygurs marry early, tend to have more children compared to the minority populations of China, and correspondently the abortion rate is lower and breast feeding time longer for Uygur women, in accordance with the results of this study. It has been reported that the divorce rate of Uygur women is higher than that of Han women primarily due to religious reasons [17].

A high cholesterol and low vegetable diet results in Uygur women having a higher BMI compared to Han women. Jun et al. [18] observed an association between polymorphism with BMI-related obesity in Uygur women. Researchers have also reported an association between BMI and high-grade BC in Uygur women [19]. As patients with a higher BMI often have increased amounts of breast tissue, it is difficult to locate neoplasms under breast tissue fat. In addition, the lack of health care coverage and screening examinations in Uygur areas, contribute to an increase in the ignorance of painless abnormal breast mass or discharge. Such situations are the primary reason for more Uygur women presenting with larger BC tumors and more incidences of positive LN

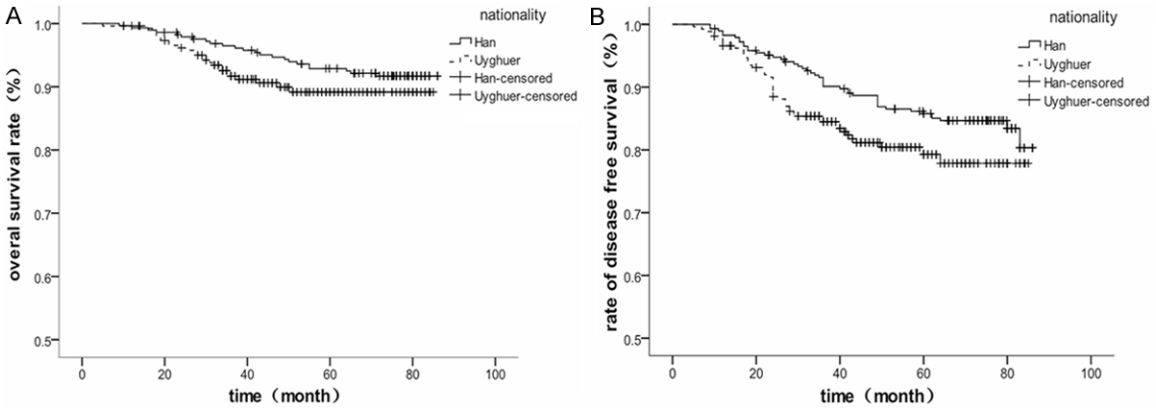

Figure 1. Kaplan Meier analysis of overall survival (OS) (A) and disease free survival (DFS) (B) in Uygur and Han breast BC patients. For DFS analysis, patients whose cancer neither progressed, nor suffered other malignancies nor died were censored on the date of the last assessment. For OS, patients who did not die or were lost to follow-up were censored on the last date they were known to have been alive.

and a subsequent lower survival rate. Methotrexate-based chemotherapy, a therapy less effective than anthrocycline chemotherapy, is the primary choice for individuals unable to afford better regimens [20]. The fact that there was more usage of methotrexate-based chemotherapy in the Uygur BC group compared to the Han BC group indicates a generally lower income population with a worse prognosis in the Uygur BC group. Simultaneously, radiotherapy was suggested according to the later stage of BC, a chief reason why more Uygur patients received radiotherapy.

Whilst a gap exists in both the OS and DFS survival curves, no statistical difference in OS was found. The 5-year OS and DFS of Uygur patients was lower than Han BC patients. The BC stage at the time of diagnosis is crucial in determining BC survival. Other factors such as treatment options and financial support; however, are also critical [21, 22]. Due to the limitations of this study, the authors were unable to conclude that OS was lower in the Uygur group compared to the Han BC group as disequilibrium of the pathologic stage existed in both groups. Furthermore, in a retrospective study, whilst the group bias is controlled, it is generally higher in the control group (Han). A strictly case-controlled study and a long-term follow-up are required.

Apart from the related promoting factors of BC, a striking pathological finding is that the Uygur group tended to be composed of only one factor. Ductal carcinoma is the most common form of carcinoma, with similar frequency, in both Uygur and Han women. Interestingly, the results of the present study showed that more medullary carcinoma was found in the Uygur compared to the Han group, this is similar to epidemiological research in Africa compared to Europe [23]. In addition, the significantly higher expression of nm23 in Uygur patients, a protecting factor of BC [16], may indicate a better prognosis for Uygur BC patients if the pathologic staging is not later than Han BC patients.

In recent years most researchers have referred to the molecular subtype, a classification based on hormone receptors and Her-2 status to indicate BC prognosis and the related systematic therapy [24, 25]. A triple negative type of BC was more prevalent in African Americans compared to the other ethnic groups studied [26]. In addition, a higher incidence of HER-2 overexpressing tumors was observed in Asian women compared to Caucasian women [27]. In the present study however, similar results between the two groups were not observed.

In addition, breast conserving surgery was low in both groups. The main reasons for altering a patient's chemotherapy regimen included progression of the disease and intolerance of the side effects associated with chemotherapy; however, this change in chemotherapy regimen did not differ between the two groups.

The majority of unfavorable factors associated with BC were manageable by Uygur patients resulting in the enhanced OS of Uygur patients. From the results of the current study, it is clear

that women should be educated about BC, a healthy diet with lower fat promoted, and screening examinations such as mammography and ultrasounds administered periodically. With such improvements, a better survival rate of Uygur BC patients is expected in the future.

Conclusions

The present study found that differing characteristics of Uygur BC patients resulted in a relatively low survival rate in this population. Further research is required to determine if the effects of the genetic and phenotypic indices of the tumor could ultimately result in a better prognosis in Uygur BC patients. Owing to the majority of the differences that exert a negative influence on survival being manageable, the survival rate of Uygur BC patients is expected to improve primarily due to enhanced education and improved health care.

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Authors' contributions

Meihui Shan, Xiaoli Wang, Gang Sun and Binlin Ma have made substantial contributions to conception and design. Meihui Shan, Xiaoli Wang, Gang Sun, Xuemei Yao, Alibiyati Ainy, Jing Ma, Chao Dong, Hongtao Li and Muzapar Abudukeremu have made substantial contributions to acquisition of data. Meihui Shan, Xiaoli Wang, Gang Sun have made substantial contributions to analysis and interpretation of data. Meihui Shan, Binlin Ma have been involved in drafting the manuscript or revising it critically for important intellectual content. All authors have given final approval of the version to be published.

Disclosure of conflict of interest

None.

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