Original Article

Quality of life in women with cervical precursor lesions and cancer: a prospective, 6-month, hospital-based study in China

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Abstract

The overall survival of patients with cervical cancer has improved due to detection at an early stage and availability of comprehensive treatments in China. As patients' lives prolonged, it is important to understand their health-related quality of life (QoL) during and after treatment. We used the EQ-5D questionnaire to assess QoL of 194 patients with cervical lesions at Sichuan University West China Second Hospital between May 2010 and January 2011. Patients were surveyed before primary treatment and at 1, 3, and 6 months after primary treatment. Results showed a consistent decline in EQ-5D scores in the spectrum of cervical lesions at each time point after treatment (all P < 0.05). For patients with precursor lesions, there was an increasing trend along the timeline of treatment (P < 0.01). For patients with early-stage cervical cancer, EQ-5D scores declined in the first month (P = 0.01) and gradually increased to higher levels at 6 months post-treatment than those before treatment (P < 0.01). EQ-5D scores followed a similar trend in patients with advanced cervical cancer (P = 0.04), though they did not statistically rebound after 6 months (0.84 ± 0.19 vs. 0.86 ± 0.11, P = 0.62). Regarding advanced cervical cancer, EQ-5D scores for women above 40 years of age appeared to recover more rapidly and reached higher levels than those for women below 40 years (P = 0.03). Caution and extra care are recommended in the early period of cervical cancer treatment given the slight deterioration in the QoL, and in particular, for younger cervical cancer patients. Our study implies that health care providers may need to improve the health-related QoL of cervical cancer patients.

Key words Cervical cancer, cervical precursor lesion, quality of life, EQ-5D, prospective study, Chinese women

Cervical cancer is the third most common gynecologic malignancy

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in China[1]. Annual absolute estimates of cases and deaths of cervical cancer were 62,000 and 30,000, respectively, in 2012[1]. Current efforts for cervical cancer prevention and control in China include mass screening in some rural areas and opportunistic screening in urban areas. Like in many developed countries^[2], the incidence and mortality of cervical cancer are expected to decline substantially now that screening techniques such as Pap smear have become available and accessible to women in China. In addition, overall survival may improve due to detection of cervical cancer at an early stage^[3] and availability of comprehensive treatments in China[4-6].

Despite major progress in treatment, cervical cancer continues to have an adverse impact on the health-related quality of life (QoL) of patients and the patients' families. Diagnosis of cervical precursor lesions or cancer is emotionally traumatic[7], and treatments such as surgery, chemotherapy, and radiotherapy further negatively impact body image, self-esteem, relationships with partners, and sexual and reproductive functions, adding to overall decrease of QoL[8]. Thus, it is important to understand the change of QoL of patients during and after treatment, and explore the factors that affect it.

The QoL of cervical cancer patients involves self-reported perception of physical, psychosocial, and sexual well-being^[9]. It can be used to evaluate the economic burden of cervical cancer as well as the economic impact of interventions such as cervical cancer screening and yet-to-be introduced human papillomavirus (HPV) vaccination in China. QoL has been tentatively studied for cervical cancer patients in China^[10], but the findings have limited application because the studies were cross-sectional and did not focus on cervical cancer lesions. Indeed, given the irrelevance of the findings, they are not even incorporated into data parameters for modeling the economic impact of screening and HPV vaccination[11,12].

To address this gap, we conducted two prospective studies on the QoL of patients with cervical lesions in a hospital-based design using the generic Medical Outcomes Study Short Form-36 (MOS SF-36)^[13] and EuroQol questionnaire (EQ-5D, renamed EQ-5D-3L in 2005)^[14]. The EQ-5D is a standardized, 5-dimensional, preferencebased, health-related QoL questionnaire designed by the EuroQol group^[14]. With its ability to generate a preference-weighted index score, it is widely recommended for use in clinical and economic evaluation^[15,16]. Overall, its responsiveness is equal to the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-30, a widely used, disease-specific, health-related QoL instrument in cancer research^[17,18]. In particular, EQ-5D is reliable and valid for the assessment of health-related QoL in patients with cervical cancer in Taiwan, in comparison with QLQ-30^[19]

The objectives of the current study were to (1) evaluate the QoL among women in mainland China with cervical precursor lesions or cancer at different stages and determine how QoL changes along the timeline of treatment, and (2) determine the influence of age on the QoL in Chinese women. We aimed to confirm earlier findings^[13] and explore the relevance of QoL of patients with cervical cancer to clinical practice.

Patients and Methods

Patients

Patients with cervical precursor lesions and/or cancer were recruited from the West China Second Affiliated Hospital between May 2010 and January 2011. They were referred to us by their attending physicians and invited to participate in our survey on a voluntary basis. Decisions to decline the invitation were respected irrespective of the reasons. All cervical precursor lesions and cervical cancers were diagnosed based on pathologic examination. The stage of cervical cancer was further identified according to the International Federation of Gynecology and Obstetrics (FIGO) staging system based on clinical examination. Patients received standard treatments according to biopsy findings, physical conditions, and fertility requirements^[13]. The study was approved by the Institutional Review Board of the Cancer Institute of Chinese Academy of Medical Sciences.

Questionnaire survey

All participants were aware of their disease condition. None had mental disease or consciousness problems. Participants were surveyed with the EQ-5D before primary treatment and at 1, 3, and 6 months after primary treatment in a face-to-face manner or by phone. The simplified Chinese version of the EQ-5D questionnaire was downloaded from the official EQ-5D website (www.eurogol.org). In brief, the questionnaire comprises a five-item descriptive system of health states and a visual analogue scale (VAS). The descriptive system covers five dimensions including mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has three levels: no problems, moderate problems, and extreme problems. Each health state can be assigned a weighted utility score based on different scoring systems. Because the Chinese utility set is not yet established, we calculated EQ-5D scores according to the classic UK preference weighting system^[20], as EQ-5D based on this scoring algorithm was validated by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ) C-30 in Chinese Taiwan^[19]. The EQ-5D VAS records self-rated health on a vertical scale with 100 representing the best imaginable health and 0 representing the worst imaginable health. The given number can be used as a quantitative measure of health outcome judged by the individual respondent.

Statistical analysis

Survey data were entered independently by two medical students in a database developed using EpiData (EpiData Association, Odense, Denmark). Inconsistencies were addressed based on original answers in questionnaires until consensus was reached. For analytic purposes, we divided all cases into the following groups: cervical precursor lesion, including cervical intraepithelial neoplasia (CIN) II and CIN III; early-stage cancer, including FIGO Ia, Ib, and IIa; and advanced (FIGO IIb⁺) cervical cancer^[3].

Data were analyzed using IBM SPSS Statistics version 19.0 (Armonk, New York, the United States). Average age and age distribution were analyzed among patients with different stages of cervical lesions by Student t test and chi-square test. A general linear model for repeated measures was used to assess the overall difference in EQ-5D scores among different time points. In addition, multiple comparisons were made among different time points for each stage of cervical lesions. One-way analysis of variance test was used to compare EQ-5D scores, and the Student-Newman-Keuls test was selected for multiple comparisons among different stages of cervical lesions at each time point. Given that age was a potential covariate for EQ-5D scores, we divided all cases into two age groups (< 40 and \geq 40 years) according to the age distribution of surveyed women and then compared EQ-5D scores for each stage at each time point using the Student t test. To tentatively confirm the validity of EQ-5D scores, the bivariate linear correlation test was used to evaluate the correlation between EQ-5D and VAS scores at each time point. Statistical significance was assessed by two-tailed test with an α level of 0.05.

Results

Patient characteristics

A total of 194 women completed the EQ-5D questionnaire at four time points, including 37 with CIN II, 41 with CIN III, 13 with FIGO Ia cervical cancer, 42 with FIGO Ib cervical cancer, 30 with FIGO IIa cervical cancer, and 31 with FIGO IIb cervical cancer. All patients were followed up fully for 6 months after primary treatment. The average age [mean \pm standard deviation (SD)] of all women was (41.4 \pm 9.6) years (range: 21–53 years). The average age was (36.2 \pm 7.6) years for women with cervical precursor lesions, (43.2 \pm 9.0) years for women with early-stage cancer, and (47.8 \pm 9.2) years for women with advanced cancer (P < 0.01 for overall comparison and P < 0.05 for multiple comparisons). The age distribution was significantly different (P < 0.01), and an increasing trend was observed in patients with a later stage of disease than in those with an earlier stage of disease (P < 0.01 by linear-by-linear association) (**Table 1**).

Comparisons of EQ-5D scores for patients with different stages of cervical lesions and at different time points

Table 2 summarizes average EQ-5D scores for patients with different stages of cervical lesions at different time points. Overall, a statistically significant difference was noted in EQ-5D scores among different groups (F = 33.9, P < 0.01) and among different time points (F = 23.4, P < 0.01) after Greenhouse-Geisser correction). There were significant differences among distinct stages of cervical lesions before primary treatment (P = 0.03) and at 1, 3, and 6 months after treatment (P < 0.01 for three time points) (**Figure 1**). Before primary treatment, EQ-5D scores were significantly higher in patients with precursor lesions than in those with cervical cancer (P < 0.05 by multiple comparisons), whereas patients with early-stage cancer only reported slightly higher EQ-5D scores than patients with advanced cancer (0.84 \pm 0.19 versus 0.83 \pm 0.20, P > 0.05). At each time point after primary treatment, multiple comparisons between groups showed that there was a consistent decline in EQ-5D scores in the spectrum of cervical lesions (P < 0.05 for multiple comparisons at each time point). Distinct patterns of change were observed in EQ-

Table 1. Age distribution of patients with different stages of cervical lesions

	Stage of lesions					
Age group	Precursor	Early stage	Advanced	Total	Р	
21–39 years	47	27	6	80	< 0.01	
40-53 years	31	58	25	114		
Total	78	85	31	194		

Table 2. EQ-5D scores of patients with different stages of cervical lesions at different time points by age

Stage	Age group (number of patients)	Timeline of treatment					
		Pretreatment	1 month posttreatment	3 months posttreatment	6 months posttreatment		
Precursor	Overall	0.90 ± 0.12	0.96 ± 0.07	0.98 ± 0.54	0.99 ± 0.02		
	< 40 years (47)	0.89 ± 0.14	0.96 ± 0.07	0.98 ± 0.06	1.00 ± 0.00		
	≥ 40 years (31)	0.93 ± 0.09	0.97 ± 0.07	0.99 ± 0.04	0.99 ± 0.04		
	Р	0.18	0.59	0.51	0.22		
Early stage	Overall	0.83 ± 0.20	0.77 ± 0.22	0.84 ± 0.20	0.94 ± 0.12		
	< 40 years (27)	0.79 ± 0.22	0.78 ± 0.20	0.85 ± 0.20	0.95 ± 0.09		
	≥ 40 years (58)	0.86 ± 0.18	0.76 ± 0.24	0.84 ± 0.20	0.93 ± 0.14		
	Р	0.16	0.73	0.80	0.56		
Advanced	Overall	0.84 ± 0.19	0.68 ± 0.32	0.75 ± 0.31	0.86 ± 0.11		
	< 40 years (6)	0.84 ± 0.13	0.63 ± 0.29	0.66 ± 0.30	0.78 ± 0.12		
	≥ 40 years (25)	0.84 ± 0.21	0.69 ± 0.33	0.77 ± 0.31	0.88 ± 0.12		
	Р	0.96	0.69	0.46	0.03		

All score values are presented as mean \pm standard deviation. All P values are for comparisons between two age groups for distinct stages of cervical lesions at different time points.

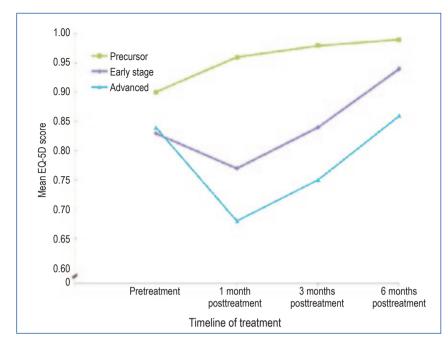


Figure 1. Distribution of EQ-5D scores for each stage of cervical lesion along the timeline of treatment. For patients with precursor lesions, EQ-5D scores followed an increasing trend along the timeline of treatment (F = 26.65, P < 0.01after Greenhouse-Geisser correction for overall comparison: P < 0.05 for pairwise comparisons). For patients with early-stage cervical cancer, EQ-5D scores declined in the first month of treatment (P = 0.01) and by 6 months, gradually increased to a higher level than that before primary treatment (P < 0.01). EQ-5D scores showed a similar trend in patients with advanced cervical cancer (F = 5.38, P < 0.01 after Greenhouse-Geisser correction for overall comparison), though scores were not statistically recovered at 6 months after treatment (0.84 \pm 0.19 vs. 0.86 \pm 0.11, P = 0.62).

5D scores along the timeline of treatment for precursor lesions and cervical cancer (**Figure 1**). For patients with precursor lesions, EQ-5D scores followed an increasing trend along the timeline of treatment (F = 26.65, P < 0.01 after Greenhouse-Geisser correction for overall comparison; P < 0.05 for pairwise comparisons). For patients with early cervical cancer, EQ-5D scores declined in the first month of treatment (P = 0.01) and by 6 months, gradually increased to a higher level than those before primary treatment (P < 0.01). EQ-5D scores showed a similar trend in patients with advanced cervical cancer (F = 5.38, P < 0.01 after Greenhouse-Geisser correction for overall comparison), though scores were not statistically recovered at 6 months after primary treatment (0.84 ± 0.19 vs. 0.86 ± 0.11 , P = 0.62).

Comparison of EQ-5D scores by age

Because the age distribution was significantly different between each two stages of lesions, we stratified the patients by age for subanalysis (**Table 2**). Our preliminary analysis showed similar trends in EQ-5D scores between women below 40 years and equal to or above 40 years old (**Figure 2**). Among women with advanced cervical cancer, EQ-5D scores for women equal to or above 40 years old appeared to recover more rapidly and reached a higher level of QoL than those for women below 40 years old (P = 0.03). However, there were no other significant differences between the two age groups for any other stage of cervical lesions at different time points (**Table 2**).

Consistency between EQ-5D and VAS scores

We also tentatively analyzed the association between EQ-5D and VAS scores. For easy comparison, we divided the VAS score by 100 (VAS/100). In general, EQ-5D and VAS scores showed similar

changes along the timeline of treatment (**Figure 3**) and correlated with each other at different time points (Pearson coefficients: 0.57 for overall analysis, and 0.38, 0.66, 0.58, and 0.51 for each time point; all P < 0.01).

Discussion

Cervical cancer affects women at a mean age of approximately 50 years^[21]. In China, mortality tends to increase at an annual rate of 4.1% in young urban women^[22]. If cured, these women may have an additional life expectancy of 25 to 30 years, and consequently they will have to suffer eventual impairment due to the malignancy and sustained treatment^[9]. As the survival of cervical cancer patients is prolonged, QoL becomes an increasingly important concern for both patients and health care providers. In the current study, we found that women with precursor lesions had higher EQ-5D scores than women with early-stage cervical cancer, whose scores, in turn, were higher than those of patients with advanced cervical malignancy within 6 months after primary treatment. In addition, EQ-5D scores for patients with cervical precursor lesions increased continuously but, in patients with either early-stage or advanced cervical cancer, declined within the first month and rebounded until the end of the 6-month follow-up.

EQ-5D scores were higher in women with precursor lesions than in those with cervical cancer, indicating that better QoL is achieved if cervical lesion is detected at an early stage. This finding was consistent with that in a sister study conducted concurrently based on MOS SF-36 in China^[13]. Cervical precursor lesions are usually asymptomatic, though there may be watery vaginal discharge or occasional spotting of blood that generally does not affect women's daily activities. In addition, these lesions are often cured with measures that are less invasive. It is thus understandable that women with precursor lesions report better QoL after primary

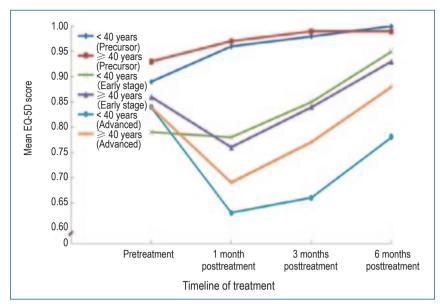


Figure 2. Comparison of EQ-5D scores between younger and older women with cervical lesions along the timeline of treatment. Among women with advanced cervical cancer, EQ-5D scores for the women equal to or above 40 years appeared to recover more rapidly and reached a higher level of QoL than those for the women below 40 years (P = 0.03). However, there were no other significant differences between the two age groups for any other stage of cervical lesions at different time points.

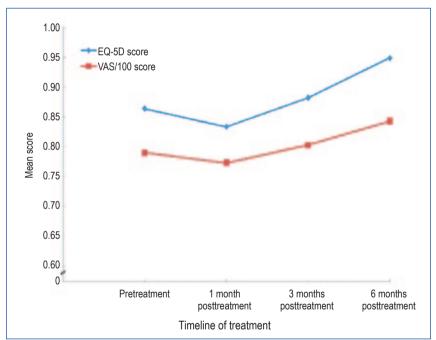


Figure 3. Comparison of EQ-5D and VAS scores along the timeline of treatment. The EQ-5D and VAS scores showed similar changes along the timeline of treatment and correlated with each other at different time points (Pearson coefficients: 0.57 for overall analysis, and 0.38, 0.66, 0.58, and 0.51 for each time point; all P < 0.01).

treatment than those with invasive lesions. Patients diagnosed with early-stage cervical cancer are usually treated with either surgery, radiotherapy, or a combination of both. Some patients also receive concurrent chemotherapy as part of curative treatment. Standard treatment for patients with advanced-stage cervical cancer is external pelvic radiotherapy combined with brachytherapy to the cervix, and in current practice, this is usually combined with chemotherapy^[9]. Different treatment algorithms affect the lives of surviving women to a varying degree. The trend is that radiotherapy is more associated with reduced QoL than surgery or chemotherapy^[9], as it is accompanied

by long-term adverse effects. Compared with early-stage lesions, advanced cervical cancer is often treated with prolonged composite modalities. It is also a larger shock than early-stage cancer, as patients may feel no hope of cure. All of these factors contribute to the low self-rated EQ-5D scores in patients with advanced cervical cancer. Of note, we observed no statistically significant differences in EQ-5D scores between patients with early-stage and advanced cancer before primary treatment. This may be explained intuitively, given that a definitive diagnosis of a cancer-related disease or a cancer is equally appalling for patients. In both cases, patients

experience a period of conflicting emotions before primary treatment, and their perception of physical, behavioral, and emotional functions and well-being is thus compromised. During this period, health care providers might play a role in alleviating the distress of patients with different stages of cervical lesions by offering extra counseling on patient concerns, giving lifestyle advice, prompting adherence to treatment, and sharing follow-up plans[8,23].

Distinct patterns of change were observed in EQ-5D scores along the timeline of treatment of precursor lesions and cervical cancer. For patients with cervical precursor lesions, EQ-5D scores showed an increasing trend within 6 months after primary treatment, whereas EQ-5D scores for patients with cervical cancer declined significantly in the first month of treatment and gradually increased in the remaining follow-up period. We propose that prescribed treatment of cervical cancer may exert a massive negative impact due to concomitant complications and adverse effects, such that this impact overshadows even perceived benefits from treatment. This explanation is reasonable given that treatments are often complicated and prolonged for cervical cancer as opposed to precursor lesions^[24]. We also noticed that EQ-5D scores at the end of the follow-up did not recover to a level statistically significantly higher than that before primary treatment. This is substantial, as we often push for robust treatment to better survival but forget to pay attention to overall QoL of cervical cancer patients. How to improve the balance between cure and QoL is thus essential in clinical practice. Given that EQ-5D scores were closely correlated with EQ-5D VAS scores in the study and that EQ-5D is well validated in a Chinese population in Taiwan^[19], we recommend that QoL measurements such as EQ-5D or other disease-specific scale may be incorporated into routine health care to monitor patient QoL. Fortunately, there is a trend that QoL measurements are included in clinical trials on strategies in treating cervical cancer, which is a good beginning for clinical practice^[9].

In our study, younger and older women showed similar change patterns of EQ-5D scores along the timeline of treatment. Two age subgroups with early-stage or advanced cervical cancer experienced a decline in scores in the immediate time and subsequently an increase until the end of follow-up, whereas two subgroups with precursor lesions showed a constant increase in scores. These results are consistent with those of overall analysis for patients with distinct stages of cervical lesions. However, we noticed that younger women (versus older women) with advanced cancer generally reported lower EQ-5D scores at each time point, especially at 6 months after primary treatment. This is consistent with previous studies showing that younger patients with cervical cancer appear to experience greater distress^[25] and that age is positively associated with physical and emotional well being [26]. Similarly, results from an analysis of QoL of patients with breast cancer suggest that younger women should be considered to be at high risk for QoL disruption and significant clinical distress^[27]. Younger patients may have a long remaining life with adverse effects and sequels of treatment. Lower self-esteem, poorer body image due to the removal of the uterus at a childbearing age, and negative impact on sexuality are apparent in these patients^[28]. Given the trend of young age at diagnosis of cervical cancer in urban women, the younger cohort should be given enough attention, and targeted interventions are recommended.

There are certain limitations in our survey that should be addressed in future studies. First, we were unable to quantify the effect of treatments and other demographic variables as a contributing factor to the variation in EQ-5D scores in the follow-up and between patients with different stages of cervical lesions. This is due to sample size limitations and incomplete information and requires efforts for a large-scale follow-up. It will be essential in the future to follow up several cohorts of patients receiving similar treatments to discriminate treatment-relevant QoL. Second, because EQ-5D is a generic QoL scale, it does not cover all major dimensions of the QoL of cervical cancer patients. In particular, sexuality as a major concern is not enquired in addition to physical and psychosocial well-being in the survey. Of note, post-treatment disruptions to sexual function often persist when psychosocial adjustment have normalized^[8]. However, in respect to clinical utility, EQ-5D may be simple and handy and be more sensitive and responsive compared with more complex cervical-cancer-specific QoL instruments such as FACT-Cx and QLQ-Cx54^[29]. Third, due to the unavailability of value set in China, we used the classic UK-based scoring algorithm to calculate the EQ-5D score. Such a value set might not reflect the social preference in China. Thus, a China-specific scoring mechanism will be necessary for future studies.

Conclusions

Overall, QoL is good in women with early-stage disease. With treatment, QoL improves continuously for patients with precursor lesions, but declines in the immediate time after treatment and increases afterwards for cervical cancer. Younger cervical cancer patients are likely to suffer more distress and QoL disruption. Our findings have significant clinical implications for patient-centered health care. Caution and extra care should be taken in the early period of cervical cancer treatment due to a slight deterioration in the QoL, and also for younger cervical cancer patients. Our study implies that resources should be mobilized to improve the health-related QoL in health care delivery for cervical cancer patients.

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