

## RESEARCH ARTICLE

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# Health-Related Quality of Life of Patients with Cervical Cancer According to the Duration of Treatment and Cancer Progression

Jooyeon Park<sup>1</sup>, Yunjung Kim<sup>1</sup>, Jimin Kim<sup>1</sup>, Sokbom Kang<sup>2</sup>, Kidong Kim<sup>3</sup>, Jong Hyeok Kim<sup>4</sup>, Hye-Sung Moon<sup>5</sup>, Eun-Ju Lee<sup>6</sup>, Soo-Young Hur<sup>7</sup>, Younhee Kim<sup>1,8\*</sup>

### Abstract

**Objective:** The purpose of this study was to assess health-related quality of life (HRQoL) in Korean patients with cervical cancer according to the duration of treatment and cancer progression of cervical cancer. **Methods:** This study included 452 outpatients with cervical intraepithelial neoplasia (CIN) or invasive cervical cancer from six tertiary hospitals in South Korea. The questionnaire included the EQ-5D-3L instrument, patients' age, cancer progression (CIN or invasive cervical cancer), treatment duration (<1 year, ≥1 year but <2 years, and ≥2 years), treatment method (surgery, chemotherapy, radiation therapy), and presence of recurrence. HRQoL indices were calculated for these independent factors, and the mean was compared using ANOVA. Multiple regression analysis was performed to analyze factors affecting HRQoL in patients with cervical cancer. **Results:** The EQ-5D index was 0.93 for patients with CIN, 0.87 for patients with invasive cervical cancer, and 0.78 for patients with recurrent invasive cervical cancer. HRQoL was significantly lower as the CIN progresses to cervical cancer. HRQoL of patients with invasive cervical cancer was lowest within 1 year of treatment in all stages. In addition, the HRQoL of patients with CIN or invasive cervical cancer who received chemotherapy and radiotherapy was lower than that of patients who underwent surgery. Multiple regression analysis showed that the HRQoL decreased significantly as increasing age, the first year of treatment after diagnosis, cancer recurrence, or chemotherapy. **Conclusion:** The HRQoL of patients with cervical cancer is affected not only by the stage of cancer progression but also by the duration of treatment and the type of treatment. As a result, when trying to apply the quality of life of patients with cervical cancer to cost-utility analysis, it is necessary to consider the duration and the type of treatment they receive.

**Keywords:** Health-related quality of life- EQ-5D- cervical cancer

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### Introduction

Cervical cancer is the fourth most prevalent cancer among women worldwide. In 2020, a total of 604,124 women were diagnosed with cervical cancer worldwide, of which 341,831 died (Sung et al., 2021). It is the 7<sup>th</sup> most prevalent cancer among Korean women, affecting 58.9 per 100,000 women in 2018 (KOSIS, 2021b). The age-adjusted cervical cancer incidence rate of Korean women was 10.5 per 100,000 in 2018 (KOSIS, 2021a), and the mortality rate was 3.5 per 100,000 women in 2019 (KOSIS, 2021d). On the other hand, the 5-year relative survival rate of cervical cancer is over 80%,

which is relatively high compared to other cancers, except for breast and thyroid cancer (KOSIS, 2021c). Thus, it is important to manage the health-related quality of life (HRQoL) of patients with cervical cancer. HRQoL can be measured using condition-specific and generic measures (Maciejewski, 2006; Brazier et al., 2016). Generic measures are comprehensive measures that assess a single aspect or multiple aspects of health-related functioning in daily life. These measures can be applied to different types of diseases, treatments, and patients. Thus, generic measures can be used to compare the effects of treatment across diseases (Maciejewski, 2006). The EuroQol EQ-5D is the most common generic

<sup>1</sup>National Evidence-based Healthcare Collaborating Agency, Seoul, South Korea. <sup>2</sup>Center for Uterine cancer, Research Institute and Hospital, National Cancer Center, Gyeonggi-do, South Korea. <sup>3</sup>Department of Obstetrics and Gynecology, Seoul National University Bundang Hospital, Gyeonggi-do, South Korea. <sup>4</sup>Department of Obstetrics and Gynecology, Asan Medical Center, Seoul, South Korea. <sup>5</sup>Department of Obstetrics and Gynecology, Ewha Womans University Medical Center, Seoul, South Korea. <sup>6</sup>Department of Obstetrics and Gynecology, Chung-Ang University Hospital, Seoul, South Korea. <sup>7</sup>Department of Obstetrics and Gynecology, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea. <sup>8</sup>College of Medicine, Inha University, Incheon, South Korea. \*For Correspondence: younhee@inha.ac.kr

measure of HRQoL and has been validated for use in patients with cancer (Lang et al., 2010; Kim et al., 2012; Schwenkglenks and Matter-Walstra, 2016; Setiawan et al., 2018). The extracted utility from the EQ-5D is widely used to calculate quality-adjusted life years (QALYs), which is used in cost-utility analysis. The guidelines for the economic evaluation of pharmaceuticals in several countries prefer cost-utility analysis using QALY (NICE, 2013; HIRA, 2021).

Many previous studies have reported the HRQoL of patients with cervical cancer using the EQ-5D. Although HRQoL has been shown to depend on the duration of treatment after diagnosis among cervical cancer patients, only a few studies have explored the HRQoL among patients with cervical cancer according to the duration of treatment after diagnosis. (Zhao et al., 2014). Therefore, this study was conducted to measure HRQoL in Korean patients with cervical cancer in relation to the duration of treatment after diagnosis and the progression of cervical cancer.

## Materials and Methods

### Participants

For this study, 452 female participants were recruited from six tertiary hospitals in Seoul and Gyeonggi-do. Patients with cervical intraepithelial neoplasia (CIN) or invasive cervical cancer who visited these hospitals as outpatients were included in the study. Patients with CIN were classified as CIN1 or CIN2/3, whereas those with invasive cervical cancer were categorized into stages I, II, or III/IV. The protocol of this survey was reviewed and approved by the Institutional Review Board of the National Evidence-based Healthcare Collaborating Agency (NECA) (NECAIRB12-007-1) and each hospital.

### Procedure and instruments

An obstetrics and gynecology specialist at each institution asked patients who met the study's inclusion criteria to participate in the survey. If the patients agreed to participate in the survey, an obstetrics and gynecology specialist filled out the medical staff entries and delivered them to the research nurse. After providing these patients with an overview of the survey, the research nurse received informed consent from the participants and conducted a face-to-face survey from October to December 2012.

The EQ-5D-3L questionnaire was used to evaluate patients with cervical intraepithelial neoplasia (CIN) or invasive cervical cancer. The EQ-5D-3L was developed by the EuroQol Group and evaluated general health status in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

The Korean version of the EQ-5D has already been validated for Korean patients with breast cancer (Kim et al., 2015). There are three levels to each dimension: no problems, some or moderate problems, and extreme problems. The EQ-5D-3L can capture 243 unique health states based on these dimensions. As a result, the EQ-5D provides a simple descriptive profile and a single HRQoL index (ranging 0–1) that may be used for cost-utility analysis (Kim et al., 2015). A high score of EQ-5D-index

indicates a high level of HRQoL. The EQ-5D valuation set established in South Korea was used to calculate the quality of life of cervical cancer patients in this study (Lee et al., 2009).

The questionnaire included the age of patients, progression of cancer (CIN or cervical cancer), treatment duration (<1 year, 1 to 2 years and  $\geq 2$  years), treatment method (surgery, chemotherapy, radiation therapy), and the presence of recurrence (yes or no).

### Statistical analysis

We first examined the distribution of each variable to analyze its general characteristics. Next, the QoL indices were calculated according to the independent variables, and the mean was compared using ANOVA analysis. Finally, we performed a multiple regression analysis to analyze the impact of patient age, disease progression, treatment method, and treatment duration on HRQoL. All analyses were performed using Stata version 13.0 (StataCorp., College Station, TX, USA). Statistical significance was set at  $P < 0.05$ .

## Results

### Participants

A total of 422 patients completed the survey. Their demographic and clinical characteristics are presented in Table 1. The 40–49 age group comprised 27.90%, followed by the 50–59 (27.40%), 30–39 (17.90%), and 60–69 (16.80%) age groups. The mean age of patients was 50.6 years (SD 12.5 years). Most of the patients (87.4%,  $N=395$ ) were diagnosed with invasive cervical cancer, and CIN was diagnosed in 12.6% ( $N=57$ ). Of those diagnosed with invasive cervical cancer without recurrence ( $N=368$ ), 66.30% had stage I ( $N=244$ ), 27.09% had stage II ( $N=96$ ), and 7.61% had stage III/IV ( $N=28$ ). Among those diagnosed with recurrent invasive cervical cancer ( $N=27$ ), 59.26% had stage I ( $N=16$ ), 18.52% had stage II ( $N=5$ ), and 22.22% had stage III/IV ( $N=6$ ). Among the patients diagnosed with CIN, most (85.96%) had CIN 2/3. Regarding the duration of treatment of patients with invasive cervical cancer without recurrence, a majority (41.85%,  $N=154$ ) underwent  $\geq 2$  years of treatment. Those treated for <1 year comprised 37.77% ( $N=139$ ), and those who were treated for 1 to 2 years comprised 20.38% ( $N=75$ ). For patients with CIN, 49.12% ( $N=28$ ) were treated for <1 year, 28.07% ( $N=16$ ) were treated for  $\geq 1$  but <2 years, and 22.81% ( $N=13$ ) were treated for  $\geq 2$  years. Among all patients in the study, a majority (64.2%) underwent surgery, 35.8% received chemotherapy, and 37.8% received radiation therapy.

### Quality of Life with different stages of cervical cancer at treatment durations

The EQ-5D index was 0.93 (SD = 0.08) for patients with CIN, 0.87 (SD = 0.12) for patients with invasive cervical cancer, and 0.78 (SD = 0.2) for patients with recurrent invasive cervical cancer (Table 2). The quality of life was significantly lower as cancer progressed ( $F=13.22$ ,  $P < 0.001$ , not reported in Table 2). The quality of life of patients with invasive cervical cancer was lowest

Table 1. General and Clinical Characteristics of the Study Participants

Variable	Categories	n	%	
Total		452	100	
Age (y)	20–29	12	2.7	
	30–39	81	17.9	
	40–49	126	27.9	
	50–59	124	27.4	
	60–69	76	16.8	
	≥70	33	7.3	
Progression of cervical cancer	CIN	Subtotal	57	100
		CIN 1	8	14.04
		CIN 2/3	49	85.96
	Cervical cancer	Subtotal	368	100
		Stage I	244	66.3
		Stage II	96	26.09
		Stage III/IV	28	7.61
	Recurrent cervical cancer	Subtotal	27	100
		Stage I	16	59.26
		Stage II	5	18.52
		Stage III/IV	6	22.22
	Treatment period after diagnosis	CIN †	Subtotal	57
<1 year			28	49.12
1 to 2 years			16	28.07
Cervical cancer		Subtotal	368	100
		<1 year	139	37.77
		1 to 2 years	75	20.38
Recurrent cervical cancer		Subtotal	27	100
		<1 year	18	66.67
		1 to 2 years	6	22.22
Treatment method ‡		Surgery	290	64.2
		Chemotherapy	162	35.8
		Radiotherapy	171	37.8

Note: †CIN, cervical intraepithelial neoplasia; ‡, Enable multiple responses

within 1 year of treatment in all stages and increased after 1 year, and showed a tendency to decrease slightly after 2 years or more except for recurrent cervical cancer. (Table 2 and Figure 1). The quality of life of patients with cervical cancer was statistically different depending on the duration of treatment, except for stage III/IV and recurrence (Table 2).

The quality of life of patients who received chemotherapy and radiotherapy was 0.83 (SD = 0.13) and 0.84 (SD = 0.15), respectively, which were lower than those of patients who underwent surgery (0.89, SD = 0.89). Patients who received surgery, chemotherapy or radiotherapy also had the lowest quality of life during the first year of treatment.

#### Factors affecting the quality of life of patients with cervical cancer

Regression analysis was performed to identify factors affecting the quality of life of patients with CIN or invasive cervical cancer. Regression analysis showed that the quality of life decreased significantly as increasing age, the first year of treatment after diagnosis, cancer recurrence, or chemotherapy. The EQ-5D index appeared to decrease step-by-step according to cancer progression, but this was not statistically significant.

### Discussion

This study aimed to estimate HRQoL in Korean patients with cervical cancer using the EQ-5D index according to the duration of treatment after diagnosis and progression of cancer. The study found that the quality of life decreased as CIN progressed to invasive cervical cancer and when cervical cancer recurred. Furthermore, the quality of life of patients who received chemotherapy and radiotherapy was worse than that of patients who underwent surgery, with the lowest quality of life occurring in the first year after diagnosis. These findings are consistent with those of previous studies involving cervical cancer patients of in China (Zhao et al., 2014) or a systematic literature review (Ceilleachair et al., 2017). However, the EQ-5D

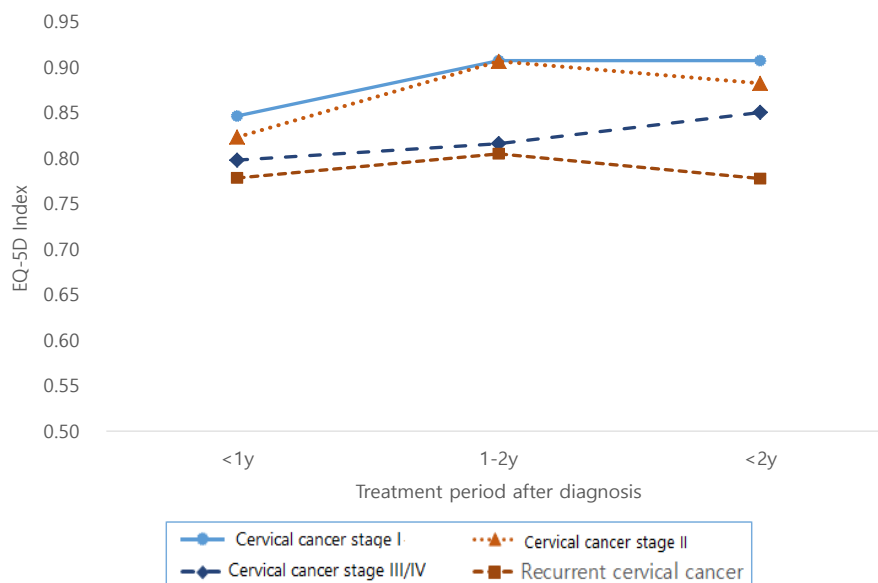


Figure 1. Quality of Life of Patients at Different Periods after Diagnosis

Table 2. Quality of Life of Patients with Different Stages of Cervical Cancer at Different Periods after Diagnosis

		N	Total	<1 year	1 to 2 years	≥2 years	p-value ‡		
			[Mean (SD)]	[Mean (SD)]	[Mean (SD)]	[Mean (SD)]			
Progression of cervical cancer									
CIN	Subtotal	57	0.93 (0.08)	0.94 (0.07)	0.93 (0.08)	0.92 (0.09)	0.743		
	CIN 1	8	0.94 (0.07)	0.95 (0.07)	0.98 (0.05)	0.84 (0.03)	0.055		
	CIN 2/3	49	0.93 (0.08)	0.94 (0.07)	0.91 (0.08)	0.94 (0.08)	0.659		
Cervical cancer	Subtotal	368	0.87 (0.12)	0.83 (0.14)	0.9 (0.1)	0.9 (0.11)	<0.001		
	Stage I	244	0.89 (0.13)	0.85 (0.16)	0.91 (0.1)	0.91 (0.1)	0.002		
	Stage II	96	0.85 (0.11)	0.82 (0.11)	0.91 (0.07)	0.88 (0.11)	0.011		
	Stage III/IV	28	0.82 (0.14)	0.8 (0.17)	0.82 (0.13)	0.85 (0.11)	0.708		
Recurrent cervical cancer		27	0.78 (0.2)	0.78 (0.22)	0.81 (0.13)	0.78 (0.23)	0.961		
Treatment method									
Surgery		290	0.89 (0.11)	0.87 (0.13)	0.9 (0.09)	0.91 (0.11)	0.02		
Chemotherapy		162	0.83 (0.13)	0.81 (0.13)	0.86 (0.12)	0.85 (0.13)	0.071		
Radiotherapy		171	0.84 (0.15)	0.81 (0.17)	0.88 (0.12)	0.87 (0.13)	0.017		

† SD, standard deviation, ‡, ANOVA tests

scores of Korean patients with cervical cancer reported in this study were generally higher than those reported in previous studies (Galante et al., 2011; Praditsitthikorn et al., 2011; Murasawa et al., 2014; Endarti et al., 2015; Jyani et al., 2020). It's unclear whether the variations in scores are attributable to cultural, behavioral, or survey period differences, or if they're due to differences in the quality of medical service provision between countries, such as pain control or side effect management. In general, however, several studies have shown that quality of life scores tend to be higher in surveys involving group of patients than those involving the general population (Galante et al., 2011; Murasawa et al., 2014).

In addition, the quality of life of patients with CIN or invasive cervical cancer was lowest in the first year of treatment in this study. Considering that the intensity of treatment at the initiation of treatment is the highest, it appears that the quality of life of patients with cervical cancer is affected not only by the stage of cancer progression but also by the time point in the duration of treatment. Therefore, when applying the quality of life to

cost-utility analysis, it may be unwise to assume that the quality of life of patients is the same every year, even for the same stage of cancer.

This study has several limitations. First, the quality of life of patients with CIN and cervical cancer was measured by dividing their duration of treatment into <1 year, 1 to 2 years, and ≥ 2 years, but it is difficult to assume that their quality of life remained the same across their entire treatment duration. According to a previous study by Zhao et al.(2014), there was a difference in the quality of life of patients with cervical cancer at 1 month after treatment initiation and at 3 and 6 months. More so, the EQ-5D index asks about the health status when the questionnaire is filled up and was, therefore, influenced by the general condition of the patients who visited as outpatients. In this study, we could not identify if the purpose of the patient's outpatient visit was to manage side effects after treatment (surgery, chemotherapy, or radiotherapy) or for a routine examination. This is a critical limitation because the purpose of the visit can influence answers to the questionnaire and, therefore, affect the quality of life scores. Compared to previous studies that investigated the quality of life of patients with cancer by cancer stage regardless of treatment duration, this study, which investigated the quality of life by treatment duration in addition to cancer stage, is considered to be improved. Future studies identifying at what point in treatment duration does quality of life significantly change are needed.

Another limitation is that this study did not sufficiently investigate sociodemographic factors that could affect the quality of life of patients with CIN and invasive cervical cancer. The quality of life of patients with cancer is affected not only by age but also by their income, education, occupation, and marital status (Han et al., 2014; Jyani et al., 2020; Kershaw et al., 2008; Park et al., 2018; Roick et al., 2019; Shao et al., 2017; Short et al., 2006; Subramaniam et al., 2018; the ACTION Study Group, 2017). In general, even if the average quality of

Table 3. Factors Affecting Quality of Life of Patients with Cervical Cancer

Variable	Coeff	p-value
Age	-0.0018	0.000
Progression of cervical cancer (ref: CIN1)		
CIN2/3	0.0002	0.996
Cervical cancer stage I	-0.0300	0.490
Cervical cancer stage II	-0.0300	0.508
Cervical cancer stage III/IV	-0.0914	0.058
Within 1 year after diagnosis	-0.0474	0.000
Recurrence	-0.0495	0.045
Surgery	0.0128	0.316
Radiotherapy	0.0028	0.855
Chemotherapy	-0.0330	0.039

Note: R-squared = 0.1672; Adj R-squared= 0.1483, F = 8.85 (p<0.001)



life is applied to the cost-utility analysis, it is necessary to identify the various individual sociodemographic factors that influence the quality of life among patients with cancer.

Finally, one of the study's limitations is that the data was collected in 2012. According to the obstetrics and gynecology specialist, there have been few therapeutic improvements in the last 10 years that could affect the quality of life of cervical cancer patients. Nonetheless, when comparing Korean clinical guidelines for cervical cancer released in 2010 and 2020 (Korean society of gynecologic oncology, 2010; Korean society of gynecologic oncology, 2020), targeted therapy (bevacizumab) and immunotherapy (pembrolizumab) have been included throughout the last decade. It is unclear whether these improvements in treatment have had an impact on the quality of life for Korean cervical cancer patients. However, given the lack of quality-of-life studies of cervical cancer patients, the findings of this study are expected to provide data to investigate the quality of life of cervical cancer patients.

In conclusion, the quality of life of patients with cervical cancer is affected not only by the stage of cancer progression but also by the duration of treatment after diagnosis and the type of treatment. As a result, when trying to apply the quality of life of patients with cervical cancer to cost-utility analysis, it is necessary to consider the duration of treatment after diagnosis and the type of treatment they receive. Meanwhile, the quality of life of patients with cervical cancer in Korea appears to be better than that in other countries. Further research is needed to investigate the reasons for this difference.

### Author Contribution Statement

The authors confirm contribution to the paper as follows: study conception and design: Jooyeon Park, Yunjung Kim, Jimin Kim, Sokbom Kang, Kidong Kim, Jong Hyeok Kim, Hye-Sung Moon, Eun-Ju Lee, Soo-Young Hur, Younhee Kim; data collection: Sokbom Kang, Kidong Kim, Jong Hyeok Kim, Hye-Sung Moon, Eun-Ju Lee, Soo-Young Hur;

analysis and interpretation of results: Jooyeon Park, Younhee Kim; Preparation of the manuscript: Jooyeon Park, Younhee Kim. All authors reviewed the results and approved the final version of the manuscript.

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### Conflict of Interest

All authors declare that there is no conflict of interest.

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