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Impact of time elapsed since diagnosis on neuropathic symptoms, sexual function, lymphedema, and overall quality of life in ovarian cancer survivors (KGOG 3068)

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Objective
To assess the impact of time since treatment on the quality of life (QOL), neurotoxicity, sexual function, lymphedema, and utility in ovarian cancer survivors.

Methods
This secondary analysis of a cross-sectional study examined the QOL, neurotoxicity, sexual function, lymphedema, and utility in 172 epithelial ovarian cancer survivors treated with first-line platinum-based chemotherapy without recurrence. Associations between time since treatment and overall QOL (National Comprehensive Cancer Network/functional assessment of cancer therapy ovarian symptom index-18 [NFOSI-18]), neurotoxicity (neurotoxicity subscale, version-4 [NTX-4]), sexual function (female sexual function index, 6-item Korean version [FSFI-6K]), lymphedema (gynecologic cancer lymphedema questionnaire [GCLQ]), and utility (EuroQol 5-dimension [EQ-5D]) were visualized using jittered box plots.

Results
Overall QOL (NFOSI-18) improved up to 3 years post-treatment (scores: 29.3 at 1 year, 28.6 at 2 years, and 26.6 at 3 years), followed by minor fluctuations over time. NTX-4 scores improved until 5 years (8.2, 7.7, 6.2, and 5.8), but remained above normal (score 0). Sexual function (FSFI-6K) increased until 3 years of age (4.6, 6.9, and 10.4 years), stabilizing at a level indicative of dysfunction (score <21). The lymphedema (GCLQ) scores fluctuated over time (4.9, 5.6, 3.3, 4.3, 5.2, and 3.8). Utility (EQ-5D index) improved up to 3 years (0.8250, 0.885, and 0.925), whereas the EQ-5D visual analog scale score increased gradually up to 5 years (71.5, 72, 73, 76, and 74), indicating ongoing recovery.

Conclusion
In ovarian cancer survivors, QOL, symptom burden, and utility gradually improved over time post-treatment but did not fully return to pre-treatment levels.

Keywords: Ovarian neoplasms; Quality of life; Neurotoxicity syndromes; Sexual dysfunction, psychological; Lymphedema

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Introduction

Ovarian cancer remains a significant contributor to global morbidity and mortality, with approximately 324,398 new cases diagnosed each year (GLOBOCON 2022) [1].

Treatment-related and disease-induced adverse effects significantly impact patients' quality of life (QOL). Studies have reported a multifaceted decline in QOL among patients with ovarian cancer, affecting various health dimensions, including physical, psychological, and sexual [2-11]. Specifically, studies have confirmed a negative impact on the QOL [11], with notable differences linked to the chemotherapy regimens used [12,13]. Furthermore, patient characteristics such as age, baseline comorbidities, and disease stage may influence QOL outcomes [11].

However, few studies have examined changes in QOL over time among ovarian cancer survivors, and the effects of time on neurotoxicity, sexual health, and lymphedema-related QOL remain underexplored [14,15]. Additionally, existing studies typically have a relatively short follow-up period, with a median of only 2 years [16]. There remains a substantial gap in understanding long-term QOL changes, particularly beyond 5 years post-treatment. This is especially important as many survivors continue to experience late or persistent effects of treatment. Our study addresses this gap by evaluating long-term QOL-related outcomes in survivors post-diagnosis, thereby providing insights into the chronic symptom burden and long-term survivorship care.

The primary objective of this study was to assess the association between the time since diagnosis and QOL in ovarian cancer survivors. Understanding how QOL changes over time is essential in real-world clinical settings. For instance, neurotoxicity, such as numbness of the hands and feet, is a common symptom among cancer survivors and a frequent concern of physicians. However, long-term follow-up studies that could provide timely trends are challenging. Given the available data, an alternative is to analyze QOL at multiple post-diagnosis time points. For instance, if neurotoxicity scores improve 5 years post-treatment compared to 1 year, it may suggest a tendency for neurotoxicity to improve over time.

Using this approach, we analyzed data from a previous study that reviewed QOL in ovarian cancer survivors at multiple time points post-diagnosis. This study aimed to examine the relationship between time since diagnosis and QOL, focusing on neurotoxicity, sexual health, lymphedema, and overall well-being.

Materials and methods

1. Study design and case selection

We conducted a secondary analysis of a previously published cross-sectional study conducted by Lee et al. [17], which aimed to validate the Korean versions of National Cancer Comprehensive Cancer Network/functional assessment of cancer therapy (FACT) ovarian symptom index-18 (NFOSI-18) and FACT/gynecologic oncology group neurotoxicity 4-item (NTX-4) questionnaires in ovarian cancer patients, examining QOL, neurotoxicity, sexual function, lymphedema, and utility in ovarian cancer survivors. The data were collected from the same study.

The survey was administered to patients with ovarian, fallopian tube, and peritoneal cancers, who visited six Korean institutions between August 2016 and October 2016. Although some surveys (NFOSI-18 and NTX-4) were performed twice at different times, only the initial survey data were included in this study. The inclusion criteria were as follows: 1) patients with epithelial ovarian cancer who had received first-line platinum-based chemotherapy and 2) patients who were recurrence-free at the time of the survey.

The exclusion criteria were as follows: 1) patients with recurrent disease at the time of the survey; 2) patients undergoing active treatment such as chemotherapy or surgery; 3) patients with non-epithelial histologies or borderline tumors; 4) individuals unable to complete the questionnaire due to cognitive or language limitations; and 5) incomplete survey responses or missing clinical data. The primary objective of this study was to examine the association between time since diagnosis and overall QOL, neurotoxicity, sexual health, lymphedema, and general well-being. In total, 172 ovarian cancer survivors were included.

2. Procedure

Data extraction: basic demographic variables (age at diagnosis, menopausal status, smoking status, alcohol consumption, height, weight, marital status, work status, family income, and exercise behavior) and disease characteristics (treatment type, cancer drug type, treatment duration, International Federation of Gynecology and Obstetrics stage, recurrence

status, and diagnosis date) were extracted and summarized from the dataset.

Scoring: scores were calculated for each questionnaire. 1) NFOSI-18 index for overall symptoms (range, 0-72; 0=no symptoms; 72=worst symptoms) [17]. 2) NTX-4 scores for neurotoxicity (range, 0-16; 0=no symptoms; 16=severe neurological symptoms) [17]. 3) Female sexual function index, 6-item Korean version (FSFI-6k) index for sexual dysfunction, with female sexual dysfunction (FSD) diagnosed at scores ≤21 [18]. 4) Gynecologic cancer lymphedema questionnaire (GCLQ) index for lymphedema, with scores ≥5 indicating lymphedema [19]. And 5) general QOL and health status were assessed using two scales: the EuroQol 5-dimension (EQ-5D) utility scores (range, 0-1; 1=full health and 0=worst health) and the EQ-5D visual analog scale (range, 0-100; 0=worst health imaginable and 100=best health imaginable) [20-22].

Analysis: associations between the time since diagnosis and QOL survey scores were analyzed using visualization. As the diagnosis time varied, the time from diagnosis to the survey also varied.

This secondary analysis used anonymized data and excluded the need for patient consent from the Institutional Review Board. The study adhered to ethical and scientific principles in line with the Korean Good Clinical Practice and the Helsinki Declaration of 2013.

3. Data analysis

The demographic and disease characteristics of the participants were analyzed using numerical data, percentages, and quartiles. Categorical variables were presented as frequency (%), whereas continuous variables were expressed as mean±standard deviation or median (range). Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Patients were stratified into six groups at these monthly intervals: 0-12, 13-24, 25-36, 37-48, 49-60, and >60 months.

A box-and-whisker plot with jittering was used to visualize each of the six scores, showing the trends over time. Whiskers represent the range (minimum to maximum) and boxes indicate the interquartile range. The black line within the box denotes the median and the white dots represent the mean. The red dots represent individual jittered data points. This analysis was conducted in Python version 3.8 (Python Software Foundation, Wilmington, DE, USA) using the Matplotlib version 3.3.2 (NumFOCUS, Austin, TX, USA) and Seaborn version 0.11.1 (NumFOCUS) libraries.

Results

The sociodemographic and clinical characteristics of the participants are summarized in Table 1. The mean age was 53.78±10.5 years, with the majority being menopausal, nonsmokers, and non-drinkers. More than half (55.8%) of the participants engaged in regular physical activity. The distribution of cancer stages was as follows: stage 1, 66/172 (38.4%); stage 2, 26/172 (15.1%); stage 3, 57/172 (33.1%); and stage 4, 21/172 (12.2%).

Table 2 presents a comprehensive overview of the symptom scales and their corresponding mean scores.

The progression of symptom scale scores over time is illustrated using box-and-jitter plots (Fig. 1). 1) Overall QOL (NFOSI-18) improved until 3 years post-treatment (29.3 at 1 year→28.6 at 2 years→26.6 at 3 years), then plateaued (26.43 at 5 years→26.52 at >5 years) Fig. 1A. 2) Neurotoxicity (NTX-4) improved until 5 years post-treatment (8.2→7.7→6.2→5.8→6.5→5.08) but did not reach normal levels (i.e., score 0) Fig. 1B. 3) Sexual life (FSFI-6K) improved until 3 years post-treatment (4.6→6.9→10.4), then plateaued at around 10, indicating FSD (score <21) Fig. 1C. 4) Lymphedema (GCLQ) scores fluctuated over time (4.9→5.6→3.3→4.3→5.2→3.8) Fig 1D. 5) EQ-5D utility index improved until 3 years post-treatment (0.8250→0.885→0.925→0.911→0.924) Fig. 1E. And 6) the EQ-5D visual analog scale (VAS) scores gradually improved until 5 years post-treatment (71.5→72→73→76→74), suggesting ongoing utility recovery Fig. 1F.

Discussion

The NFOSI-18 and NTX-4 scales are robust tools for assessing the overall QOL and neurotoxicity in ovarian cancer cohorts, with evidence of reliability and validity in diverse cultural populations, including Koreans [17,23]. In our study, the overall QOL, measured by the NFOSI-18, improved until 3 years post-treatment, plateauing at around a score of 26. However, neurotoxicity, as measured by NTX-4, improved until 5 years post-treatment, reaching a score of 5 but did not

Table 1. Demographic and clinical characteristics (n=172)

Variable	Value
Clinical characteristic	
Age of patient at diagnosis	27 to 81 (53.78±10.5)
Disease duration (months)	
0-12	37 (21.5)
13-24	46 (26.7)
25-36	34 (19.8)
37-48	21 (12.2)
49-60	11 (6.4)
>60	23 (13.4)
FIGO stage at diagnosis	
1	66 (38.8)
2	26 (15.3)
3	57 (33.5)
4	21 (12.4)
Demographic characteristic	
Marital status	
Never married	16 (9.3)
Married	143 (83.1)
Divorced	5 (2.9)
Widowed	8 (4.7)
Education level	
None	2 (1.2)
Elementary	12 (7.1)
Middle	14 (8.2)
High	56 (32.9)
College or more	86 (50.6)
Job	
Yes	56 (32.6)
No	116 (67.4)
Income	
Equal or less than 2 million won/month	32 (19.5)
2-3 million/month	30 (18.3)
3-4 million/month	31 (18.9)
4-5 million/month	31 (18.9)
More than 5 million/month	40 (24.4)
Smoking	
Current smoker	3 (1.7)
Past smoker	7 (4.1)
Never	162 (94.2)
Alcohol	
Two to three times/week	2 (1.2)
Once a week	15 (8.8)
None	154 (90.0)
Exercise	
Yes	96 (55.8)
No	76 (44.2)
Menopausal status	
Yes	155 (90.1)
No	17 (9.9)

Values are presented as range (mean±standard deviation) or number (%).
FIGO, International Federation of Gynecology and Obstetrics.

return to normal levels (Fig. 1A, B). This aligns closely with findings from a multicenter, population-based registry study assessing the impact of chemotherapy-induced peripheral neuropathy (CIPN) on QOL, which showed that CIPN symptoms decreased up to 3 years post-treatment but persisted beyond this period, continuing to impact QOL [9]. CIPN is a serious adverse event that can substantially affect the QOL of cancer survivors undergoing chemotherapy. With increasing cancer incidence, improved survival rates, and increased chemotherapy use, along with a lack of effective treatments or preventive measures, CIPN has become a major challenge for cancer survivors [24,25]. Recent interventions, such as duloxetine, have demonstrated efficacy in reducing CIPN symptoms, although its broader uptake remains limited. Furthermore, lifestyle interventions, such as structured physical activity, neuromodulation therapy, and acupuncture, are being actively explored as adjunct strategies for managing neuropathy in cancer survivors [24,25]. Researchers have extensively studied the impact of neuropathy in patients with ovarian cancer treated with platinum-based chemotherapy. However, additional factors may contribute to neurotoxicity, presenting potential intervention targets. Stevinson et al. [26] suggested that physical activity might have an inverse relationship with peripheral neuropathy. Additionally, factors such as older age and comorbidities including diabetes, obesity, and cancer stage at diagnosis have been shown to affect various QOL domains and potentially influence neuropathy [27]. In our study, the average age was 53.7 years, most diagnosed at stage 1 (38.4%) and followed by stage 3 (33.1%).

Table 2. Symptom scale scores

Symptom scale	Range in the study	Normal range
Disease-related physical and emotional symptoms, side effects of treatment, and functional well-being (NFOSI-18)	0 to 46 (28.14±8.72)	0-72
Neurotoxicity (NTX-4)	0 to 15 (6.89±4.23)	0-16
Sexual dysfunction (FSFI-6K)	0 to 23 (8.04±7.01)	>21
Lymphedema (GCLQ)	0 to 19 (4.9±3.8)	<5
Overall assessment		
EQ 5D utility index	-0.081 to 1.00 (0.886±0.129)	0-1
EQ 5D VAS scale	30 to 100 (73.59±15.62)	0-100

Values are presented as range (mean±standard deviation).
NFOSI-18, National Comprehensive Cancer Network/functional assessment of cancer therapy ovarian symptom index-18; NTX-4, neurotoxicity 4-item scale; FSFI-6K, female sexual function index, 6-item Korean version; GCLQ, gynecologic cancer lymphedema questionnaire; EQ-5D utility index, EuroQol 5-dimension utility index; VAS, visual analog scale.

The majority were non-smokers and non-drinkers, with over half reporting regular exercise; however, neurotoxicity scores did not return to normal after 5 years (Table 1). Further research should target specific subgroups to better understand how comorbidities affect the NFOSI-18 and NTX-4 over time.

The mean FSFI-6k score was initially 8, gradually improving over time but plateauing near 10 after 5 years, which still indicates FSD (Table 2, Fig. 1C). A study by Kim et al. [15] comparing QOL and sexuality between ovarian cancer survivors and healthy individuals found a mean FSFI score of 19.9 in survivors, with significantly higher rates of vaginal dryness, poorer social functioning, and financial difficulties. Similarly, Domenici et al. [5] reported FSFI scores indicative of FSD in patients with ovarian cancer undergoing primary chemotherapy, multimodal treatment, primary chemotherapy, and multimodal treatment. Sexuality is a multifaceted concept encompassing the physical, psychological, and social dimensions essential to an individual's life [5,28]. Previous research has indicated that a substantial proportion of gynecological cancer survivors often experience symptoms such as reduced sexual desire, pleasure, and activity [5,29]. Sexual dysfunction in patients with ovarian cancer can stem from various aspects of treatment, including oophorectomy, which disrupts hormone production and leads to vaginal atrophy, dyspareunia, dryness, mood swings, and chronic fatigue from chemotherapy. Nerve injury and the extent of surgery were also contributing factors. Psychological factors such as anxiety, depression, and altered body image arise from cancer stigma and surgery. Additionally, in Asian patients, reluctance toward sexual activity due to misconceptions about recurrence and discomfort in discussing sexual issues, often deprioritized in cancer care, reflects cultural attitudes and suggests areas to target for improving FSFI scores [30]. Issues, such as vaginal dryness, which is significantly more prevalent in cancer survivors than in healthy individuals, can be managed with lubricants or estrogen gels. We acknowledge the limitations of our study and recommend further research that accounts for these factors as it remains inconclusive whether sexual function normalizes over time.

Addressing lymphedema in survivors of ovarian cancer is a major healthcare challenge. Current research has mainly focused on breast cancer-related lymphedema, limiting the development of effective management strategies for patients with ovarian cancer. The GCLQ was developed for evaluating lower extremity lymphedema [19]. In our study, the GCLQ scores of the ovarian cancer survivors exhibited a waxing and waning pattern (Fig. 1D), indicating a chronic condition that warrants further focus on preventive and therapeutic strategies. Similarly, a study by Iyer et al. [31] found a high prevalence of lower limb edema in ovarian cancer survivors, with high body mass identified as a significant predictor. Despite emerging advances in treatment options, including complete decongestive therapy, laser therapy, physical therapy, manual lymphatic drainage, compression bandaging, advanced pneumatic compression devices, exercise, skincare, and surgical management, such as lymphovenous anastomosis, lymphedema remains a persistent issue that hinders recovery and affects overall QOL [32,33]. Our study reiterates this finding, highlighting the need for further research to tailor interventions specifically for ovarian cancer-related lymphedema and

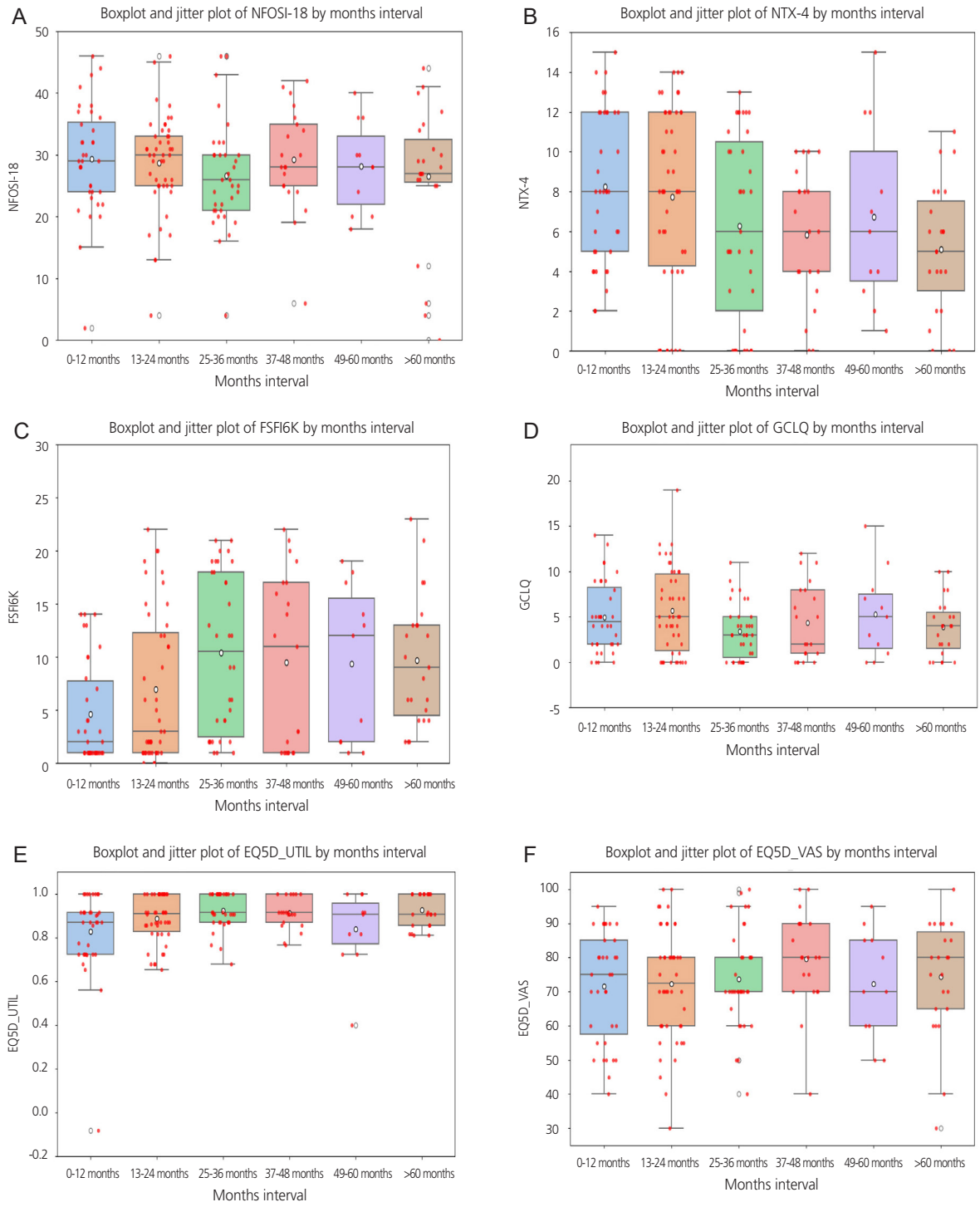

Fig. 1. (A) Box-and-jitter plot of NFOSI-18, (B) NTX-4, (C) FSFI-6K, (D) GCLQ, (E) EQ-5D utility, and (F) EQ-5D VAS scores across time intervals. NFOSI-18, National Cancer Comprehensive Cancer Network/functional assessment of cancer therapy (FACT) ovarian symptom index-18; NTX-4, FACT/gynecologic oncology group neurotoxicity 4-item; FSFI-6K, female sexual function index, 6-item Korean version; GCLQ, gynecologic cancer lymphedema questionnaire; EQ-5D utility, EuroQol 5-dimension utility; VAS, visual analog scale.

explore additional treatment options that can reduce physical and psychosocial impacts and improve QOL.

The literature offers a nuanced view of health-related QOL trajectories measured by the EQ-5D utility scale and EQ-5D VAS scores during and after treatment. In ovarian cancer survivors, these scales typically show a decline during and shortly after treatment, with gradual improvement over time; however, this recovery varies across QOL domains, and factors such as body mass index and physical activity can influence the extent of improvement [34,35]. In our study, both the utility index and VAS score showed progressive increases over time but did not reach the maximum scale values (Fig. 1E, F). Factors contributing to improved QOL include effective management of physical symptoms, psychological support, and social reintegration. Identifying the predictors of QOL recovery can help tailor interventions for those most in need. A limitation of our study is that as it was a cross-sectional study, it did not involve serial measurements in the same individuals. Consequently, the observed trends over time may reflect cohort differences rather than longitudinal changes. While the cross-sectional design enables a snapshot across various time points, longitudinal follow-up is necessary to confirm the true temporal trajectories in QOL outcomes.

In conclusion, the effects of time on neuropathy, lymphedema, sexual health, and the overall QOL in ovarian cancer survivors are complex and vary among individuals. Our findings suggest that QOL, symptom burden, and utility gradually improve post-treatment, but do not reach full recovery. Ongoing medical follow-ups, tailored rehabilitation, psychological support, and effective symptom management may contribute to improved long-term outcomes.

Future research should further investigate these relationships and develop targeted interventions to address the diverse needs of ovarian cancer survivors. Comprehensive survivorship programs must encompass physical, psychological, and social recovery to improve well-being and QOL and foster more effective and compassionate care strategies.

Conflicts of interest

The authors declare no conflicts of interest.

Ethics approval

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (IRB No. B-2202-741-102). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments.

Patient consent

The requirement for informed consent was waived by the Institutional Review Board of Seoul National University Bundang Hospital due to the retrospective nature of the study.

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