The influence of adverse effects on quality of life in gynecologic cancer survivors

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INTRODUCTION

The incidence of gynecological cancer (GC) has increased in recent years in Japan, with an estimated 30,964 newly diagnosed patients in 2009.1 Treatment of GC includes, in most cases, radical surgery, and depending on tumor stage and additional risk factors, adjuvant chemotherapy (Cx) and/or radiotherapy (RT). Treatment of GC often has adverse effects, including urological, bowel complications and lower extremity lymphedema (LEL).2-10 Because bothersome symptoms, including swelling, pain, numbness, and deteriorated functioning, lymphedema has been recognized to have adverse effects on patients quality of life (QOL). Such changes of adverse effects are likely to reduce QOL underlying physical well-being (PWB), social well-being (SWB), emotional well-being (EWB), and functional well-being (FWB). However, QOL and adverse effects have not been sufficiently investigated in GC patients.
One of the most frequently used QOL measurement tools is the Functional Assessment of Cancer Therapy (FACT) scale. It consists of a general form, FACT-G, evaluating PWB, SFWB, EWB, and FWB. The questionnaire is easy to understand and can be completed in a short period of time. This tool has been validated in a number of clinical studies.\textsuperscript{11}

The true incidence of LEL after treatment for GC is unknown, although previously reported estimates range from 1.2\% to 39.1\%.\textsuperscript{2-6} The variation in the prevalence of LEL may mainly be attributed to differing surgical and/or radiological treatments. Most studies have found that adjuvant radiation therapy is a significant risk factor for the development of LEL.\textsuperscript{4-7} Previously, our team reported that LEL occurred in 24.3\% with the cervical cancer (CC) patients.\textsuperscript{8} LEL may occur from as early as immediately after treatment to several years after treatment. Several studies have demonstrated that approximately 75\% of LEL cases occurred within the first year after treatment.\textsuperscript{6,9} The prevalence of LEL and its association with various risk factors are not presently well understood. Several studies have demonstrated that a 5-year urinary tract or gastrointestinal complication rate of 9.3\%, and 5-year rectal complication rate of 16\% in patients treated with RT on CC.\textsuperscript{10,11} The aim of this study is to assess correlations between QOL and adverse effects of pre-treatment and post-treatment with GC patients.

\textbf{MATERIALS AND METHODS}
Study population

The study enrolled 75 patients who had been treated for GC patients in the Department of Obstetrics and Gynecology of Okayama University Hospital. Patients of GC had some treatment strategies. 75 patients who had been treated by simple hysterectomy (SH)/modified radical hysterectomy (mRH) with/without bilateral salpingo-oophorectomy (BSO) (n=2), SH/mRH with/without BSO and pelvic lymphadenectomy (PLN) (n=5), Radical hysterectomy (RH) with/without BSO and PLN (n=6), concurrent chemoradiotherapy (CCRT) / radiotherapy (RT)(n=15), or RH with/without BSO and PLN +CCRT/RT or adjuvant Cx (n=7) on CC; SH/mRH with BSO (n=4), SH/mRH with BSO and PLN (n=13), SH /mRH with BSO, PLN and PAN (n=3), SH/mRH with BSO, PLN, and adjuvant Cx (n=7), SH with BSO, PLN, PAN and adjuvant Cx (n=3) on endometrial cancer (EC); SH with BSO and partial omentectomy (OMT)(n=1), SH with BSO, PLN, PAN and OMT(n=1), SH with BSO, PLN, PAN, OMT and neo-adjuvant or adjuvant Cx (n=8) on ovarian cancer (OC).

RT patient received with a combination of external irradiation and intracavitary brachytherapy (ICBT) with curative intent. RT was delivered at 2.0 Gy per fraction once daily, 5 days per week, over 5 weeks. The median dose to the whole pelvis was 50.0 Gy and ICBT as the high dose rate was 24 Gy/4 times. For 14 CCRT patients were treated RT with cisplatin (CDDP; 40 mg/m2 infusion weekly for six cycles). For EC and OC patient, adjuvant Cx was used depending the FIGO stage, grade, patient preference and physician discretion.
Our standard Cx consisted of paclitaxel (175 mg/m$^2$ infused over 3 hours) and carboplatin (dosed for an area under the curve of 5) for 3–8 cycles. Each treatment of GC is listed in Table 1.

Questionnaires and clinical data from medical records were collected. The questionnaires were distributed to eligible women who had been treated from Aug 2012 and Oct 2015. All participants were informed about the survey by their consultant doctors and provided written informed consent to participate in this study. All answers were voluntary. Completed questionnaires were collected using in-hospital collection boxes. This study protocol was approved by the Institutional Review Board of Okayama University Hospital (Epidemiology; No.846). QOL was measured by the FACT-G, a valid and reliable 27-item questionnaire evaluating PWB, SWB, EWB, and FWB. The FACT-G provides a generic core of questions that are often combined with cancer site-specific questionnaires.$^{12-13}$ FACT-G was performed questionnaires at pre-treatment, at least 6 weeks after treatment (post1-treatment), 3 or 6 months after treatment (post2-treatment).

The symptoms of LEL, severe gastrointestinal symptoms (SGS), and dysuria were collected from medical records. LEL was essentially classified according to the stages identified by the International Society of Lymphology (ISL), which are as follows: stage 0, refers to a subclinical condition where swelling is not evident despite impaired lymph transport; stage I, represents an early and subsides with limb elevation; stage II, denotes
tissue swelling with signs of pitting and the minimal reduction in swelling after limb elevation; late stage II, the limb may or may not pit as tissue fibrosis supervenes; and stage III, the occurrence of lymphostatic elephantiasis where pitting is absent and trophic skin changes such as acanthosis, fat deposits and warty overgrowths appear. In this study, LEL was defined as present when it was stage II, late stage II, or stage III. SGS and dysuria were evaluated and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In this study, SGS (gastrointestinal hemorrhage, ileus, intestinal obstruction) and dysuria (hematuria, urinary retention) were classified as present when they were at least grade II.

Statistical analysis

Differences between groups were analyzed using the Student t-test for continuous variables or the Mann–Whitney U test when a normal distribution was not assumed (nonparametric test). Contingency tables were adopted to compare categorical variables. Pearson χ² test was used to test for significance. All analyses were performed using SPSS 20.0 software (SPSS, Chicago, IL, USA) and P values less than 0.05 were considered significant.

RESULTS
In total, 147 patients who underwent pretreatment GC patients were identified in our cancer registry. After excluding unsuitable patients, 75 GC survivors responded to the questionnaires at the time of diagnosis (Figure 1). Patients’ characteristics are summarized in Table 1. The median age at the time of diagnosis was 56.5 years (Range; 26-87 years). Body Mass Index (BMI) was <18.5 (n = 4, 5.3%), 18.5-24.9 (n = 46, 61.4%), 25.0-29.9 (n = 18, 24.0%), 30.0-34.9 (n = 6, 8.0%), and 35.0-39.9 (n = 1, 1.3%). A total of 54 patients (72%) were married, and 60 patients (80%) had children. The diagnoses were CC patients (n=35, 46.7%), EC patients (n=30, 40.0%), and OC patients (n=10, 13.3%). More patients had early-stage cancer (n = 66, 88.0%) than advanced-stage cancer (n = 9, 12.0%). 12 patients (16.0%) were smoker, and 23 patients (30.6%) drink alcohol. A high percentage of patients had undergone only surgery (n = 32, 42.7%); other patients had undergone surgery and Cx (n = 22, 29.3%), surgery and CCRT/RT (n = 6, 8.0%), and CCRT/RT (n = 15, 20.0%).

Treatment for GC patients often has adverse effects, including LEL, dysuria, and SGS (Table 2). LEL was occurred four patients (5.3%) on stage I and five patients (6.7%) on stage II with 75 GC patients. Dysuria was occurred eight patients (10.7%) and SGS was occurred six patients (8.0%) on 75 GC patients. LEL make worse influence for cancer survivor’s QOL than other adverse effects. By each disease distinction, LEL occurred in five patients (14.3%) in CC patients, two patients (6.7%) in EC patients, two patients (20.0%) in OC patients. All
patients with dysuria and SGS were CC patients. Dysuria occurred in eight patients (22.9%), and SGS occurred in six patients (17.1%) in CC patients. All patients with LEL underwent surgery including lymph node dissection. Four patients were treated with adjuvant Cx, one patient was treated with adjuvant RT, and 4 patients have no adjuvant treatment. Furthermore, double adverse effects were occurred four patients (5.3%) with 75 GC patients. Double adverse effects have LEL plus dysuria (n=3, 4.0%) and LEL plus SGS (n=1, 1.3%).

Their mean FACT-G score values at the pre-treatment, post1-treatment, and post2-treatment with 75 GC patients were PWB score 4.51, 5.71, 4.74; SWB score 24.8, 23.3, 22.3; EWB score 8.51, 7.54, 6.51; FWB score 18.9, 18.28, 19.6. We examined whether associated with each adverse effects (LEL, dysuria, and SGS) and FACT-G score (PWB, SWB, EWB, and FWB score) at the pre-treatment, post1-treatment, and post2-treatment. Figures.2 shows the distribution of cases scored for LEL, dysuria, SGS examined according to FACT-G score with GC or CC patients. For all 75 GC patients, LEL patients shows significant lower QOL than no LEL patients in PWB at post1-treatment (p=0.026), and EWB at post2-treatment (p=0.020). Moreover, LEL patients shows significant lower QOL than no LEL patients in PWB at pre-treatment and post1-treatment (p=0.019 and p=0.010), and EWB at pre-treatment, post1-treatment and post2-treatment (p=0.016, p=0.007 and p=0.016) with 35 CC patients. However, dysuria and SGS showed no association with FACT-G score with 35 CC patients.
We examined whether associated with the number of adverse effect patients and FACT-G score at the pre-treatment, post1-treatment, and post2-treatment (Figure .3). Double adverse effect (LEL plus dysuria or SGS) patients shows significant lower QOL than no and single adverse effect patients in PWB at post1-treatment and post2-treatment (post1; \( p=0.049 \), \( p=0.001 \), post2; \( p=0.002 \), \( p=0.028 \)), and no adverse effect in EWB at post1-treatment (\( p=0.017 \)) with 75 GC patients. Moreover, double adverse effect patients shows significant lower QOL than no adverse effect patients in PWB at post1-treatment (\( p=0.001 \)), and single adverse effect patients in PWB at post2-treatment (\( p=0.006 \)) with 35 CC patients. Double adverse effect patients shows significant lower QOL than no adverse effect patients in EWB at post1-treatment and post2-treatment (\( p=0.023 \) and \( p=0.029 \)) with 35 CC patients. Single adverse effect patients shows significant lower QOL than non adverse effect patients in SWB at post1-treatment and post2-treatment (\( p=0.012 \) and \( p=0.025 \)) with 35 CC patients.

**DISCUSSION**

Cancer treatment options are improving, and the number of cancer survivors thus continues to grow. The disease and its treatment give rise to a multitude of symptoms and substantial impairments in domains of QOL. It is important to consider the effects of treatment not only on survival but also on the QOL of cancer survivors. This is the first study to evaluate the correlations between QOL and adverse effects of GC patients.
In particular, urological and bowel complications and LEL are major adverse effects of lymphadenectomy and RT for GC patients. Eifel et al. reported that 9.3% of CC patients who receive RT and survive for 5 years after treatment have major urinary tract or gastrointestinal complications. Sakata et al. reported a 5-year rectal complication rate of 16% in patients treated with RT on CC. Although previously reported estimates range from 1.2% to 39.1% of LEL with GC patients. Hareyama et al. reported an overall incidence of LEL of 21.8% (stage 1, 60%; stage 2, 32%; and stage 3, 8%) with CC patients. Previously our reported that LEL occurred in 24.3% in CC patients.

In this study, we investigated correlations between the most commonly recorded complications, namely SGS (8.0%), dysuria (10.7%), and LEL (12.0%) with GC patients. Furthermore, adverse effects occurred such as SGS (17.1%), dysuria (22.9%), and LEL (14.3%) with CC patients. Changes of adverse effects are likely to reduce QOL underlying PWB, SWB, EWB, and FWB. In breast cancer, the lymphedema and debilitating effects on QOL have only been extensively assessed survivors, and these studies have focused on uncomfortable symptoms, as well as physical, psychological, and social functioning. We investigated the QOL such as PWB, SWB, EWB, FWB and adverse effects with GC patients. PWB and EWB of LEL patients were significantly lower QOL than no LEL patients with GC and CC patients. However, dysuria and SGS showed no association with lower QOL with CC patients. Furthermore, increase adverse effects were reduced QOL underlying PWB and
EWB with GC patients. Interestingly, this study has revealed that reduce QOL such as emotional and physical associated with symptom of adverse effects.

We acknowledge that our study has some limitations. The number of patients was relatively small, and the duration of follow-up was relatively short. Further studies with more patients and longer follow-up periods would provide more definitive data to clarify the significance of our findings.

In conclusion, we found that reduce QOL such as emotional and physical associated with symptom of adverse effects with GC patients. It is important to consider the effects of radical therapy not only on survival but also on the QOL of GC survivors.

References


