Clinicopathological Risk Factors Affecting Sexual Function after Radiotherapy for Cervical Cancer Patients

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Abstract

Aim: To specify the clinicopathological risk factors that influence sexual function after radiotherapy for cervical cancer.

Methods: This observational and cross-sectional study includes a population of 60 adult women diagnosed with stage I to III cervical cancer who underwent radiotherapy. Sexual function was assessed using a self-reported standardized questionnaire, the Female Sexual Function Index (FSFI). Age, clinical stage, tumor diameter, type of radiotherapy, use of hormone replacement therapy, and period of time elapsed since the completion of radiotherapy at the time of data collection were documented using participants' medical records. Multivariate logistic regression was used to identify independent risk factors for decreased sexual function.

Results: The median age of participants was 53 years (Interquartile range, IQR, 45-60 years). Using the FSFI total score compared by variable, sexual dysfunction was significantly more prevalent among women in FIGO stage III than those in stage I /II (P = 0.038), and at ≥ 12 months after the completion of radiotherapy than at < 12 months after completion (P = 0.008). Multivariate analysis revealed that sexual morbidity was significantly more likely in stage III women (OR 4.60, 95% CI, 1.07, 24.39, P = 0.040), or where radiotherapy had occurred more than 12 months before (OR 4.78, 95% CI, 1.17, 25.20, P = 0.028).

Conclusion: FIGO stage III and a period of ≥ 12 months after radiotherapy are associated with reduced sexual function. In medical consultations with women in these categories, adequate treatment should be provided where appropriate.

Keywords: Cervical cancer, Radiotherapy, FIGO stage I-III, Sexual function, FSFI

Abbreviations: FSFI: the Female Sexual Function Index; FSD: Female Sexual Dysfunction; HRT: Hormone Replacement Therapy; EBRT: External Beam Radiotherapy Technique; HDR-ICBT: High-Dose-Rate Intracavitary Brachytherapy; FIGO: the International Federation of Gynecology and Obstetrics; RT: Radiotherapy alone; CCRT: Concurrent Chemoradiotherapy
Introduction

In Japan, 9,794 women were diagnosed with cervical cancer in 2008 and 2,712 women died of the disease in 2012 [1]. Surgery and radiotherapy are the basic treatment modalities for cervical cancer, but since 1999, concurrent chemoradiotherapy has been recommended as the standard treatment for locally advanced cancers [2,3]. The number of surviving patients has now increased, as has the prevalence of late radiation-induced side effects [4,5]. After radiotherapy for cervical cancer directly affecting sexual organs and hormonal status, all are susceptible to a high risk for sexual compromise. Both the reproductive organs and hormones are affected, exposing patients to a high risk of female sexual dysfunction (FSD), resulting from both physical and psychological changes. Previous studies have found that radiotherapy for cervical cancer results in FSD [6-8], which is defined as disorders of libido, arousal, orgasm, and sexual pain [9,10]. Sudden premature ovarian failure and vaginal shortening and stenosis after radiotherapy results in dyspareunia (sexual pain disorders) [11-13]; dyspareunia influences FSD affecting approximately 43% of women under the age of 60 in the U.S and contributing to personal psychological distress [14,15] or poor body image [16]. In addition, the associated psychological impact of the disease, combined with the physical sensations from the disease itself and the treatment side effects, may contribute to both a lower interest in sex, and consequently, a reduction in the frequency of sexual activity.

Very little attention has been placed on the sexual difficulties that women can experience after radiotherapy to the sexual organs [17]. In our previous study in 2014, by Female Sexual Function Index (FSFI) self-reported questionnaires, there was a significant difference in median (range) FSFI total score in patients after RT or RS and healthy women. The median FSFI total score in patients after RT was significantly lower than that in healthy women. Six sexual domains (desire, arousal, lubrication, orgasm, satisfaction, pain) were all significantly affected in patients after RT (The International Journal of Gynecological Cancer. 2014; 24: 800-805) [18]. However, to the best of our knowledge, only a few studies have evaluated how sexual dysfunction after radiotherapy is associated with multiple clinical factors, such as age, clinical stage, tumor diameter, type of radiotherapy, hormone replacement therapy (HRT), and the period after completion of radiotherapy. Clarifying the clinicopathological factors associated with FSD could lead to the development of more accurate interventions for cervical cancer survivors.

The aim of this study was to specify the clinicopathological factors that influence sexual problems after radiotherapy for cervical cancer by the use of a globally validated questionnaire.

Materials and Methods

This observational and cross-sectional study used a standardized questionnaire, the Female Sexual Function Index (FSFI). All participants were outpatients at the University of the Ryukyus Hospital who had undergone definitive pelvic radiotherapy or concurrent chemoradiotherapy for cervical cancer and had follow-up appointments between June 2011 and April 2012. Women were excluded from the study for the following reasons: presence of metastases or recurrence; treatment with postoperative adjuvant radiotherapy or radiotherapy for hemostasis during the study period; no sexual partner; psychiatric disorder; current use of antidepressant or psychotropic medicine; history of depression; alcohol or drug addiction; major hematologic, renal, or hepatic abnormalities; uncontrolled diabetes; serious cardiovascular disease; pre-existing health problems; and a physical or psychological handicap. The study was reviewed and approved by the institution's Ethics Committee. Written informed consent was obtained from all participants prior to the study.

In planning this research, we estimated that at least 43% of women (by analysis of data from the National Health and Social Life Survey, a probability sample study of sexual behavior in a demographically representative, 1992 cohort of U.S. adults) [14] would demonstrate FSD at enrollment. A sample size of participants was defined as being large enough to achieve a 43% incidence rate with a statistical power of 80% and a confidence level of 95%.

All participants were treated with anterior-posterior and posterior-anterior parallel-opposed ports or a 4-field external beam radiotherapy technique (EBRT). A 50 Gy dose of EBRT was delivered in 25 fractions. The center shield (4 cm wide at the midline) was set up after delivering 20-40 Gy. High-dose-rate intracavitary brachytherapy (HDR-ICBT) was delivered once per week at a fractional dose of 6 Gy and given 3 or 4 times at point A. Patients treated with concurrent chemoradiotherapy received cisplatin 20 mg/m² for 5 days every 3 weeks or 40 mg/m² weekly concomitantly with radiotherapy. A dilator for protecting vaginal contracture or shortening after radiotherapy was not used as a standard practice. Clinical stage was determined according to the International
Federation of Gynecology and Obstetrics (FIGO) 1994 classification system. Participants were asked about their use of HRT. Conjugated estrogens or estradiol with and without medroxyprogesterone acetate were used. All participants underwent a standardized evaluation for sexual function by the FSFI which focuses on arousal, desire, lubrication, orgasm, satisfaction, and pain [19].

FSFI is a brief, multidimensional self-reporting instrument to assess sexual function occurring over the previous 4 weeks in women. The scale consists of 19 items and has received initial psychometric evaluation by Rosen et al. [19], in addition to studies related to its reliability, convergent validity, and discriminant validity [20]. The FSFI has been validated for internal consistency and test-retest reliability, which are shown to be within the acceptable range. It provides a total score as well as domain scores in six areas: Desire (2 items), Arousal (4 items), Lubrication (4 items), Orgasm (3 items), Satisfaction (3 items), and Pain (3 items). Response options were organized according to a Likert-type scale of 1 to 5 for items 1, 2, 15, and 16. For the remaining items, the response options ranged from 0 to 5, because the option “no sexual activity” was included. The score of each domain is obtained by adding individual scores, then multiplying the obtained score by the corresponding factor. The total score (full scale score or overall score) is then obtained by adding together all the scores of each domain. The measurement of total sexual function can range between 2 and 36; a low score indicates the existence of multiple problems related to sexual function, and a high score represents good sexual function. In the present study, we used the published FSFI to distinguish women with or without FSD. Participants signed a written informed consent and completed the FSFI questionnaire (Refer to [18]).

Data were analyzed using JMP (ver. 14.2; SAS Institute Inc., Cary, NC, U.S.). Age, FIGO stage, tumor diameter, type of radiotherapy, HRT, and the time period since the completion of radiotherapy were expressed as observation numbers and percentages. The chi-square test was used for categorical variables. The patient variables: age significance and time period elapsed since the completion of radiotherapy at data collection, FSFI total score and each domains’ sexual functional score status were evaluated by Mann-Whitney U test to investigate the difference in the groups between the FSFI total score ≤ 5 and > 5, which were categorized by a median score. The age variable was divided into two, with 53 years old being the median score. The time period passed since the completion of radiotherapy at the time of data collection variable was divided into two groups: < 12 months and ≥ 12 months,

![Figure 1: Flow chart of participant data collection.](image-url)

The inclusion and exclusion process of the study participants shows the selection of cervical cancer participants. *HRT, Hormone replacement therapy.

Using the FSFI total score and based on receiver operating characteristics analysis (ROC), and the area under the curve (AUC, 0.627).

The results are presented as the median and interquartile range. In the univariate analysis for the FSFI total score and subscale scores by variables, the P values are from the Mann-Whitney tests analyzed. Univariate and multivariate logistic regression analysis was used for factors predicting FSD after radiotherapy. P values < 0.05
were considered significant. Sample size calculation used the EPI-INFO 7.0 statistical package.

**Results**

A flow chart of participant FSFI data collected is shown in figure 1. During the study period, 119 patients received radiotherapy at our institution, and 60 eligible patients met the inclusion criteria. Eligible patients were classified in groups according to their FSFI total score, either ≤ 5 (50%, n = 30), or > 5 (50%, n = 30), and comparisons were made between the groups.

The clinicopathological characteristics of the study patients are listed in table 1. The median (Interquartile range, IQR) age of all cervical cancer participants was 53 (45-60) years. In addition, the median (IQR) age of patients with an FSFI total score of ≤ 5 and > 5, was 51 (42-60) years, and 55 (46-60) years, respectively. Fourteen of the 30 patients (47%) in the ≤ 5 group were older than 53 years and 53% in the > 5 group. The FIGO stage distribution was as follows: in the ≤ 5 group, 11, 9, and 10 patients in stages I, II, and III, respectively; in the > 5 group, 13, 13, and 4 patients, respectively. There was therefore a higher proportion of stage III patients in the FSFI total score ≤ 5 group ($P = 0.169$). The median (IQR) period after treatment completion was 30 (11-58) months. We observed a significantly higher number of patients in the > 5 group who had completed the treatment 12 months prior to data collection ($P = 0.006$). No significant differences in characteristics were observed in age, tumor diameter, type of radiotherapy, and HRT use.

FSFI median (IQR) total score among all participants in stage I–III were 5.0 (3.6-16.7) (Table 1). Though it is not in the table here, the FSFI median subscale scores in stage III / I–III were 1.2 (1.2-2.0) / 1.8 (1.2-2.4) for Desire, 0 (0-1.0) / 0 (0-2.3) for Arousal, 0 (0-0.6) / 0 (0-3.3) for Lubrication, 0 (0-0.8) / 0 (0-3.2) for Orgasm, 2.4 (1.6-2.5) / 2.4 (2.4-3.6) for Satisfaction and 0 (0-0.6) / 0 (0-1.6) for Pain. The FSFI median subscale scores except Desire and Satisfaction in stage III as well as all patients in stage I–III were all zero. And then there are no significant different subscale score except Satisfaction between in stage III and in stage I and II. The median (IQR) for Satisfaction in stage III was significantly lower than in stage I and II ($p = 0.013$); Refer to [18] about the FSFI subscale score in stage I / II.

In univariate analysis for FSFI total score by variable (Figure 2), sexual function was not influenced by age, tumor diameter, type of radiotherapy, or HRT, but the median FSFI total score was significantly lower in women with FIGO stage III ($P = 0.038$) and in those who completed the survey > 12 months after treatment completion ($P = 0.008$).

Univariate and multivariate logistic regression analysis for factors predicting female sexual dysfunction after radiotherapy is shown in table 2. In univariate analysis, only those more than 12 months after the completion of radiotherapy (OR 6, 95% CI, 1.63, 29.13, $P = 0.006$) are shown to be independent risk factors for sexual morbidity. However, in multivariate analysis, stage III (OR 4.60, 95% CI, 1.07, 24.39, $P = 0.040$) and more than 12 months after the completion of radiotherapy (OR 4.78, 95% CI, 1.17, 25.20, $P = 0.028$) are shown to be independent risk factors for sexual morbidity.

**Table 1:** Participant characteristics.

| Characteristics | FSFI total score ≤ 5 (n = 30) | FSFI total score > 5 (n = 30) | P-value |
|-----------------|-------------------------------|-------------------------------|---------|
| Age (years)     |                               |                               |         |
| Median          | 51                            | 55                            | 0.553   |
| IQR             | 42-60                         | 46-60                         |         |
| ≤ 53            | 16                            | 14                            | 0.606   |
| > 53            | 14                            | 16                            |         |
| Clinical stage  |                               |                               |         |
| (FIGO1997)*     |                               |                               |         |
| I               | 11                            | 13                            | 0.169   |
| II              | 9                             | 13                            |         |
| III             | 10                            | 4                             |         |
| Tumor diameter  |                               |                               |         |
| ≤ 4 cm          | 10                            | 8                             | 0.573   |
| > 4 cm          | 20                            | 22                            |         |
| Radiotherapy    |                               |                               |         |
| RT              | 7                             | 3                             | 0.161   |
| CCRT            | 23                            | 27                            |         |
| HRT (yes)       | 7                             | 10                            | 0.39    |
| Months after treatment |             |                               |         |
| Median          | 37                            | 23                            | 0.09    |
| IQR             | 17-70                         | 5-57                          |         |
| < 12            | 3                             | 12                            | 0.006   |
| ≥ 12            | 27                            | 18                            |         |
| Total FSFI      |                               |                               |         |
| Median          | 3.6                           | 15.5                          | < 0.001 |
| IQR             | 3.6-4.2                       | 6.0-22.1                      |         |
RT, radiotherapy alone, CCRT, concurrent chemoradiotherapy. FIGO, International Federation of Gynecology and Obstetrics, HRT, hormone replacement therapy. FSD, Female sexual dysfunction, FSFI (Female sexual function Index) median (IQR, interquartile range) total score among all participants were 5.0 (3.6-16.7). *Patients who had stage I / II disease in this current study were included in the manuscript as follows: Int J Gynecol Cancer, 2014; 24(4):800-5[18].

**Discussion**

If the previous FSFI total score of 26.55 is taken as the optimal cut-off score for sexual dysfunction [21], the FSFI total scores after radiotherapy in our study, with a median of 5.0, IQR, 3.6-16.7 in stage I-III were shown to be markedly low. Using both univariate for FSFI total score by variable and multivariate logistic regression analysis, multivariate analysis revealed that sexual morbidity was significantly more likely in stage III women, or where radiotherapy had occurred more than 12 months before.

Regarding domains, among all participants, not only in stage I and II, but also III terribly compromised their sexual functions except in the domains of Desire and Satisfaction. Frumovitz et al. [22] reported FSD using FSFI, and investigated stage IA and IB cervical cancer patients (37 surgery, 37 radiotherapy, and 40 controls). They showed that all domains of sexual function (except Desire) were significantly lower in patients treated with radiotherapy. Damage to the pelvic splanchnic nerve, fibrosis of the vagina and the paravaginal soft tissue by radiotherapy, results in sexual insensitivity and pelvic pain, or pain during sexual intercourse. In addition, radiotherapy can cause early menopause by halting the production of sex hormones by the ovaries, leading to vaginal atrophy and dyspareunia [23,24]. Saewong S et al. [25] reported that there was a significant reduction in the frequency of sexual intercourse after radiotherapy in cervical cancer survivors, and this was significantly correlated with the FIGO stage. However, Rodrigues et al. [26] found no statistically significant differences in sexual function in stage IB2- IVA cervical cancer patients treated with pelvic radiotherapy. In our institution, radiotherapy was performed as previously described, and the median cumulative biologic effective dose at point A (EBRT + ICBT) was 64.8 Gy10 (range: 48-76.8 Gy10) for early disease, and 76.8 Gy10 (range: 38.4-86.4 Gy10) for advanced disease [27]. It is possible that this dose could be related to the fact that greater rates of sexual dysfunction were reported in women in FIGO stage III than in stages I / II of the disease. These results suggest the necessity of treating vaginal dryness and vaginal dilatation after radiotherapy, particularly in women with an advanced stage disease.

Using both univariate and multivariate analysis, our study revealed that the other risk factor for sexual dysfunction was that at the time of data collection a period of ≥ 12 months had elapsed since the completion of radiotherapy. Schover et al. [23] reported that in patients...
with cervical cancer who underwent radical hysterectomy and radiotherapy alone, significantly more problems (such as dyspareunia, postcoital bleeding, or painful penetration) were reported in patients 1 year after the termination of treatment, although at six months there was no difference in the numbers reporting problems between all the cancer treatment groups. Jensen et al. [12] researched 118 patients treated with radiotherapy for cervical cancer over a 2 yr period, using the Sexual function Vaginal changes Questionnaire (SVQ), and found that approximately 85% had low or no sexual interest. In particular, 12 months and longer after the termination of treatment, there was an increase in the number of women reporting feelings that their vagina was too small during intercourse. This feeling became increasingly bothersome, causing a lack of sexual activity, and dyspareunia was frequently observed. They suggested that FSD after radiotherapy alters sexual behavior because of the insidious changes relating to fibrosis that occur between 6 months and 1 year after treatment. It is, therefore, very important to prevent these changes soon after the completion of radiotherapy.

In relation to HRT after radiotherapy, results from previous reports are conflicting. Jensen et al. [12] reported that although lubrication, dyspareunia, orgasm, sexual satisfaction, and vaginal dimensions were not significantly related to HRT intake, patients receiving HRT had a significantly lower risk of having reduced sexual interest and of becoming sexually inactive. Denton et al. [13] reported that vaginal estrogens were effective in reducing dyspareunia and alterations in the vaginal epithelium and prevented vaginal narrowing. Although we initially hypothesized that hormonal status would play an important role in changing sexual function after treatment for cervical cancer, we could not find any relationship between HRT and FSD. Lack of attention to hormone related variables such as onset, type of HRT, and iatrogenic menopause after radiotherapy may have blunted the positive protective impact of HRT on sexual function. Therefore, it is considered necessary to conduct a prospective study of sexual function that includes an evaluation of hormonal status.

### Table 2: Univariate and multivariate logistic regression analysis for factors predicting female sexual dysfunction after radiotherapy.

| Variable                        | N    | Ref | N    | Univariate analysis | Multivariate analysis |
|---------------------------------|------|-----|------|----------------------|-----------------------|
|                                |      |     |      | Crude OR (95%CI)     | *P-value              |
|                                |      |     |      | *P-value             | Adjusted OR           |
|                                |      |     |      |                      | (95%CI)               | ‡P-value               |
| Age (years)                     | 30   | ≤ 53| 30   | 0.77 (0.28, 2.11)    | 0.605                 |
| 53<                             |      |     |      |                      | 0.29 (0.05, 1.31)     | 0.109                  |
| FIGO stage                      | 14   | I /II| 46   | 3.25 (0.94, 13.28)   | 0.064                 |
| III                             |      |     |      |                      | 4.60 (1.07, 24.39)    | 0.04                   |
| Tumor diameter (cm)             | 42   | ≤ 4 | 18   | 0.73 (0.23, 2.20)    | 0.573                 |
| 4<                              |      |     |      |                      | 0.64 (0.12, 3.48)     | 0.602                  |
| Radiotherapy CCRT               | 50   | RT  | 10   | 0.37 (0.07, 1.48)    | 0.161                 |
|                                |      |     |      |                      | 0.23 (0.02, 1.82)     | 0.169                  |
| HRT No                          | 43   | Yes | 17   | 1.64 (0.53, 5.30)    | 0.389                 |
|                                |      |     |      |                      | 2.44 (0.53, 12.09)    | 0.251                  |
| Months after treatment ≤ 12     | 45   | < 12| 15   | 6.13 (1.63, 29.13)   | 0.006                 |
|                                |      |     |      |                      | 4.78 (1.17, 25.20)    | 0.028                  |

OR, odds ratio, CI, confidence interval, Ref, Reference.

*The results obtained from logistic regression analysis indicating risk factors for sexual dysfunction.

‡P-value of whole model test was 0.0170. Female sexual dysfunction was categorized by the total score: ≤5 (Yes) or >5 (No). OR revealed Yes/ No.

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patients’ individual influences from their surroundings, or their relationship with partners. Because of these issues, our results may not be generalizable with other populations of cervical cancer patients.

**Conclusion**

Female sexual morbidity following cervical cancer treatment should be managed with interventions, [17] including counseling by specialists. It is also considered that women should receive routine clinical assessments to assess any sexual dysfunction and the rehabilitation necessary after receiving radiotherapy, and that these should be targeted at women according to their FIGO staging and the length of time since they completed radiation therapy.

**Declaration**

**Ethics approval and consent to participate**

This study protocol was reviewed and approved by the University of the Ryukyus Review Board, and written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

**Consent for publication**

We give our consent for information about ourselves and our article to be published in Current Opinion in Gynecology and Obstetrics.

**Competing interest**

The authors declare that there are no conflicts of interest.

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**Authors’ contributors**

YH participated in the conception and design, acquisition of data, analysis and interpretation of data, drafting the article, revising it for intellectual content, and final approval of the completed article. TO participated in acquisition of data, revising it for intellectual content, and final approval of the completed article. SU participated in the conception and design, analysis and interpretation of data, revising the article for intellectual content, and final approval of the completed article.

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