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Radiation therapy is not an independent risk factor for decreased sexual function in women with gynecologic cancers

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ABSTRACT

Aim: To evaluate the associations of external beam radiation therapy (EBRT) and intracavitary brachytherapy (IB) with decreased sexual function.

Background: There's inconsistent evidence on whether radiation for gynecologic cancers has an impact on sexual health. IB, an underutilized treatment modality, is thought to have less adverse effects than EBRT.

Materials and methods: A cross-sectional study examining decreased sexual function following radiation for gynecologic cancers. A decrease in sexual function was measured as a change in the Female Sexual Function Index (FSFI) from before to after treatment, with a significant decrease determined by Reliable Change Index Statistic (RCIS). Chi-square and *t*-tests were employed.

Results: 171 women completed the survey; 35% ($n=60$) received radiation, of whom 29 received EBRT and IB (48%), 15 EBRT alone (25%), 16 IB alone (27%). Women who received radiation had similar rates of decreased sexual function as women who did not (47% vs. 38%, $P=0.262$). EBRT and IB had similar rates of decreased sexual function compared to women with no radiation (50% vs. 38% $P=0.166$ and 47% vs. 38% $P=0.309$). Women experiencing decreased sexual function were more likely to be under 50 years old (OR 5.4, 95%CI 1.6–18.1), have received chemotherapy (OR 5.7, 95%CI 1.4–22.9), and have cervical cancer (OR 7.8, 95%CI 2.1–28.8).

Conclusions: Treatment with EBRT or IB does not appear to impair sexual function in women with gynecologic cancer. Age less than 50, concurrent chemotherapy, and cervical cancer may place women with gynecologic cancer at higher risk for decreased sexual function following radiation.

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1. Background

There were an estimated 105,890 new cases of gynecologic cancers in 2016 with approximately 30,890 deaths. As treatments for gynecologic cancers are advancing, patient survivorship continues to increase, with 5-year survival rates for cervical and endometrial cancer surpassing 70% and 80%, respectively.[1,2] With this increasing survivorship, a greater focus on quality of life (QOL) is imperative for patients who have survived their gynecologic cancers and respective treatments. Sexual health is an important component of the quality of life, encompassing patients' intimate relationships, personal body image and pleasure sensations, as well as their reproductive and physical functions.[3,4] Multiple studies have shown that patients with gynecologic cancers are at increased risk for declining QOL and impaired physical and sexual function.[3–6]

Currently, there is inconsistent evidence as to whether radiation therapy, in particular, has an impact on sexual health.[6] Significant prospective evidence exists that radiation therapy can be used to optimize treatment for women with gynecologic cancers, and there is also significant evidence that radiation therapies have risks of both acute and long term side effects, including dermatitis, mucositis, bowel and bladder symptoms, infertility, and vaginal stenosis.[6–8] It is unclear whether radiation therapy and these side effects impact the patient's overall sexual function. Few studies have looked at the relationship between radiation therapy and quality of life or sexual function. These studies have produced contradictory results on whether radiation therapy, itself, is associated with impaired sexual function and whether factors like diagnosis, type of radiation treatment and age have an association with declining quality of life or impaired sexual function in women with gynecologic cancers.[6,8]

2. Aim

This study aimed to examine radiation therapy, both external beam radiation therapy (EBRT) and intracavitary brachytherapy (IB), and its relationship with sexual health in order to better determine predictors of decreased sexual function following treatment. We had two main hypotheses: first, that radiation therapy, EBRT and IB would have similar rates of sexual dysfunction following treatment, and second, that concurrent chemotherapy and age less than 50 would predict higher rates of decreased sexual function following radiation therapy.

3. Material and methods

Institutional Board Approval was obtained at all sites for this multi-institutional, cross-sectional study. The study population included female cancer survivors who were treated at the gynecological cancer clinics at the University of Colorado Hospital and Denver Health medical center from September 2013 through December 2015. Inclusion criteria included age 18–89 years, a diagnosis of gynecologic malignancy, and treatment at one of the respective institutions. The study was available in English and Spanish, allowing for the inclusion of both English and Spanish speaking patients.

A cross-sectional study design was employed to assess sexual function in the female cancer survivors receiving treatment at the participating research institutions. The primary outcome analyzed was decreased sexual function following treatment. Participants were found through the gynecologic clinical practices of the participating research institutions, and administered a study survey either in person, by mail, or by an encrypted email. The study survey document included demographics, cancer diagnosis, sexual practice questions, and a sexual function questionnaire called the Female Sexual Function Index (FSFI). The FSFI includes 19 questions measuring sexual function, and has been validated for use in clinical trials. The survey was administered following completion of cancer treatment, and patients were asked to answer the sexual function questionnaire twice, once pertaining to their sexual function prior to treatment and once pertaining to their sexual function following treatment. A decrease in sexual function was measured as a change in the FSFI from before to after treatment. A Reliable Change Index Statistic (RCIS) was used to determine that a significant decrease in sexual function was a 5.8-point decrease in the FSFI.

Baseline characteristics between the radiation therapy and no radiation therapy cohorts were compared with chi square analysis. Rates of decreased sexual function were then compared between women who received radiation therapy and those who did not using chi-square and *t*-tests ($n = 171$). A bivariate analysis, again using chi-square and *t*-tests, was then performed on the sample of women who received radiation ($n = 60$). This analysis was performed with the primary outcome of decreased sexual function in order to determine which demographic and treatment variables had an association with decreased sexual function. Variables that were found to have a significant association in this bivariate analysis were then introduced into a multivariate logistic regression model to better determine independent associations with decreased sexual function. For all values, a P of <0.05 was determined to be statistically significant.

4. Results

A total of 409 women receiving treatment for gynecologic cancer at the University of Colorado Hospital and Denver Health medical center were approached for recruitment. Of these 409 women, 258 (63%) were enrolled in the study and 171 (42%) completed the pre- and post-treatment FSFI surveys. Of these 171 patients included in our analysis, 60 (35%) underwent treatment with radiation therapy, 29 of whom were treated with both EBRT and IB, 15 EBRT alone and 16 IB alone. In total, 44 women received EBRT and 45 women received IB. Women who received radiation therapy differed from those who did not in cancer diagnoses (endometrial cancer 53.3% vs. 33.3%, ovarian cancer 8.3% vs. 50.0%, cervical cancer 30.0% vs. 5.4%, $P < 0.001$), rates of surgery (78.3% vs. 97.3%, $P < 0.001$) and rates of chemotherapy (73.3% vs. 52.3%, $P = 0.007$) (Table 1).

Women who received radiation therapy had similar rates of decreased sexual function as women who did not receive radiation therapy: 47% of women receiving any type of radiation

Table 1 – Baseline characteristics of gynecologic oncology patients who did and did not receive radiation therapy, evaluated with chi square analysis.

Characteristic	Women with no radiation $n = 91$ Mean ± SD or %	Women with radiation $n = 60$ Mean ± SD or %	P-value
Age (years)	54.4 ± 12.3	54.0 ± 12.2	0.813
Age ≥50 years	79 (71.2%)	41 (68.30%)	0.699
Premenopausal at diagnosis	59 (69.4%)	28 (73.7%)	0.630
Race/ethnicity			0.429
White, non-Hispanic	93 (83.8%)	50 (83.3%)	
White, Hispanic	12 (10.8%)	8 (13.3%)	
African American	2 (1.8%)	2 (3.3%)	
Other	4 (3.6%)	0 (0%)	
Diagnosis			0.000
Endometrial	37 (33.3%)	32 (53.3%)	
Ovarian	56 (50%)	5 (8.3%)	
Cervical	6 (5.4%)	18 (30.0%)	
Other Gynecologic	12 (10.8%)	5 (8.3%)	
Stage ≤2	61 (56.5%)	30 (51.7%)	0.328
Primary disease	63 (73.3%)	32 (74.4%)	0.783
Active disease at time of survey	41 (41.4%)	21 (36.8%)	0.574
Surgical Management	108 (97.3%)	47 (78.3%)	0.000
Chemotherapy	58 (52.3%)	44 (73.3%)	0.007
BMI (kg/m^2)			0.063
<23	21 (19.6%)	20 (34.5%)	
23–29	43 (40.2%)	23 (39.7%)	
>30	43 (40.2%)	15 (25.9%)	
Relationship >10 years	73 (74.5%)	36 (72%)	0.745

therapy as part of their treatment had decreased sexual function following treatment, while 38% of women with no form of radiation therapy had decreased sexual function after treatment ($P = 0.262$). More specifically, women receiving IB had similar rates of decreased sexual function as women receiving no radiation therapy (47% vs. 38%, $P = 0.309$), and women receiving EBRT also had similar rates of decreased sexual function as women receiving no radiation therapy (50% vs. 38%, $P = 0.166$).

Among women who received radiation therapy for gynecologic cancers ($n = 60$), bivariate analysis revealed that neither IB nor EBRT were associated with higher rates of decreased sexual function (OR 1.7, 95%CI 0.3–3.9, $P = 0.803$ and OR 1.7 95%CI 0.5–5.4, $P = 0.854$, respectively). A treatment regimen combining IB and EBRT was also not a predictor of higher rates of decreased sexual function following treatment (OR 1.8, 95%CI 0.6–5.0, $P = 0.293$). The analysis showed that the two treatment modalities had similar rates of decreased sexual function following treatment (IB 21.4% vs. EBRT 25.0%, $P = 0.606$) (Table 2).

The bivariate analysis also revealed that among women who received radiation therapy ($n = 60$), those who had decreased sexual function were more likely to be under 50 years old (OR 5.4, 95%CI 1.6–18.1, $P = 0.006$), have received chemotherapy as part of their treatment regimen (OR 5.7, 95%CI 1.4–22.9, $P = 0.014$), or have a diagnosis of cervical cancer vs. endometrial cancer (OR 7.8, 95%CI 2.1–28.8, $P = 0.002$). There

Table 2 – Associations with decreased sexual function among women treated with radiation therapy for gynecologic cancer.

Characteristic	Radiation and decreased sexual function $n = 28$ Mean ± SD or %	Radiation and no decrease in sexual function $n = 32$ Mean ± SD or %	Odds ratio (95%CI)	P-value
Age (years)	**49.5 ± 11.9**	**57.9 ± 11.3**		**0.007**
Age ≥50 years	**50.0%**	**84.4%**	**5.4 (1.6–18.1)**	**0.006**
Premenopausal at diagnosis	66.7%	78.3%	0.56 (0.13–2.39)	0.428
Race/ethnicity				
White, non-Hispanic	82.1%	84.4%	ref	
White, Hispanic	17.9%	9.4%	2.0 (0.4–9.1)	0.039
African American	0.0%	6.3%	–	
Diagnosis				
Endometrial	28.6%	75.0%	ref	
Ovarian	17.9%	0.0%	–	
Cervical	**46.4%**	**15.6%**	**7.8 (2.1–28.8)**	**0.002**
Other Gynecologic	7.1%	9.4%	6.0 (0.5–75.3)	0.165
Stage ≤2	60.7%	40.6%	1.7 (0.6–5.4)	0.333
Primary disease	42.9%	62.5%	0.5 (0.1–2.0)	0.327

Table 2 (*Continued*)

Characteristic	Radiation and decreased sexual function $n=28$ Mean ± SD or %	Radiation and no decrease in sexual function $n=32$ Mean ± SD or %	Odds ratio (95%CI)	*P*-value
Active disease at time of survey	38.5%	35.5%	1.1 (0.39–33)	0.816
Surgical management	78.6%	78.1%	1.0 (0.3–3.5)	0.967
Chemotherapy	**89.3%**	**59.4%**	**5.7 (1.4–22.9)**	**0.014**
IB	75.0%	75.0%	1.7 (0.3–3.9)	0.803
EBRT	78.6%	68.8%	1.7 (0.5–5.4)	0.854
Combined IB + EBRT	53.6%	43.8%	1.8 (0.6–5.0)	0.293
BMI (kg/m^2)				
≤23	42.9%	25.0%	ref	
23–29	32.1%	43.8%	0.4 (0.1–1.5)	0.175
30–39	10.7%	15.6%	0.4 (0.1–2.2)	0.287
≥40	10.7%	12.5%	0.5 (0.9–2.9)	0.436
Radiation type				
IB only	21.4%	31.3%	ref	
EBXRT only	25.0%	25.0%	1.5 (0.3–6.1)	0.606
IB and EBXRT	53.6%	43.8%	1.8 (0.5–6.2)	0.362

Bold value indicates a *P*-value less than 0.05.

Table 3 – Multivariate logistics model for associations for decreased sexual function among women treated with radiation therapy.

	Odds ratio	95%CI		*P*-value
		Lower	Upper	
Step 1a				
Age <50	7.344	1.533	35.179	0.013
Cervical Cancer	1.258	0.74	2.141	0.397
Chemotherapy	5.969	1.59	22.405	0.008
Step 2a				
Age <50	6.311	1.393	28.599	0.017
Chemotherapy	5.903	1.582	22.022	0.008

was no difference in BMI, race, or menopausal state between the women with and without a decrease in sexual function following radiation therapy. There was also no difference in stage of disease, active disease state, or surgical management of disease between the women with and without a decrease in sexual function (Table 2).

In a subsequent multivariate logistic regression model, decreased sexual function had independent associations with concurrent chemotherapy treatment (OR 6.31, 95%CI 1.39–28.6, $P=0.017$) and age less than 50 (OR 5.90, 95%CI 1.58–22.0, $P=0.008$). Decreased sexual function was not found to be independently associated with a diagnosis of cervical cancer (OR 1.26, 95%CI 0.74–2.14, $P=0.397$) (Table 3).

When looking at specific characteristics of the radiation therapy, the total mean dose of both IB and EBRT was similar in women with and without a decrease in sexual function following treatment (24.6 ± 8.7 Gy vs. 26.6 ± 16.7 Gy, $P=0.641$ and 49.5 ± 15.6 Gy vs. 48.3 ± 9.8 Gy, $P=0.818$, respectively). Additionally, women with and without a decrease in sexual function were equally likely to receive EBRT to the whole pelvis (OR 2.9, 95%CI 0.5–17.1, $P=0.216$), lymph nodes (OR 0.8, 95%CI 0.2–2.9, $P=0.714$), or directly to a mass (OR 1.0, 95%CI 0.1–17.1, $P=1.00$) (Table 4). Women with and without a decrease in sexual function also had statistically similar rates of receiving tandem and ovoid IB vs. vaginal cuff IB (OR 1.5, 95%CI 0.5–5.0, $P=0.511$) (Table 5).

5. Discussion

Women being treated for gynecologic cancers are at risk for declining sexual health following treatment; however, our findings indicate that radiation therapy does not independently contribute to decreased sexual function. In the present study, women with gynecologic cancers who underwent treatment with radiation therapy had similar rates of decreased sexual function as women whose treatment regimens did not include radiation therapy. Our findings also indicated that EBRT and IB individually do not seem to contribute to decreased sexual function in women with gynecologic cancer: women who received either of these treatment modalities had similar rates of decreased sexual function following treatment compared to each other and to women who did not receive radiation therapy as part of their treatment.

Table 4 – Associations of location of EBRT with decreased sexual function.

Location of EBRT	All women with EBRT	Decreased sexual function $n=22$	No decrease in sexual function $n=22$	Odds ratio (95%CI)	*P*-value
WPRT	84.1%	90.90%	77.30%	2.9 (0.5–17.1)	0.216
Lymph nodes	29.5%	27.30%	31.80%	0.8 (0.2–2.9)	0.714
Mass	4.5%	4.50%	4.50%	1.0 (0.1–17.1)	1.00

Table 5 – Associations of location of IB with decreased sexual function.

Location of IB	All women with IB $n = 45$	Decreased sexual function $n = 21$	No decrease in sexual function $n = 24$	Odds ratio (95%CI)	P-value
Vaginal cuff	62.2%	12 (57.1%)	16 (66.7%)	ref	–
Tandem and ovoid	37.8%	9 (42.9%)	8 (33.3%)	1.5 (0.5–5.0)	0.511

In our study, all cases of IB were treated using high dose rate (HDR) with a source of Iridium 192. EBRT cases were all image guided with either 3D with electronic portal imaging or intensity modulated radiation therapy (IMRT) with daily cone bema CT techniques. All post-operative patients were treated with IMRT. A larger, multi-institutional study would be beneficial in allowing for evaluation of a possible association between different radiation techniques and decreased sexual function.

Although not clinically significant to patients in this trial, radiation changes to the vaginal mucosa are described in the literature, particularly with the higher doses associated with cervical cancer treatment.[9] The high turnover rate of vaginal mucosa cells contributes to the appearance changes in the mucosa, yet clinical consequences can be minimized by respecting tolerances of the normal tissue. All patients in this study were treated within published dose-volume histogram constraints for vaginal tolerance, respecting the lesser tolerance of the more distal mucosa.[10,11] Additionally, all patients are provided with vaginal dilators and educated about their use and importance, to minimize strictures that may impact future sexual function.[12]

Although we found that radiation therapy, itself, does not appear to be an independent risk factor for decreased sexual function, our study did find that there are factors that are associated with a higher risk of decreased sexual function following radiation therapy. Based on our bivariate analysis, age less than 50, treatment with chemotherapy, and a diagnosis of cervical cancer have significant associations with decreased sexual function among patients treated with radiation therapy. This same bivariate analysis demonstrated that pre-menopausal state, BMI, type of radiation therapy (EBRT or IB), total dose of radiation, location of EBRT or IB, primary vs. recurrent disease, and active disease state were not associated with decreased sexual function. A subsequent multivariate logistic regression model further evaluated age less than 50, treatment with chemotherapy, and diagnosis of cervical cancer for true independent associations with decreased sexual function. Through this model, age less than 50 and treatment with chemotherapy were shown to be independent predictors for decreased sexual function following radiation therapy, while cervical cancer was not found to be an independent predictor.

Further evaluation needs to be performed in order to evaluate why age less than 50 and chemotherapy are predictors of decreased sexual function following radiation therapy. However, there is literature that has looked at the relationships of both age and chemotherapy with sexual dysfunction. Women of younger age have been found to have increased desire, arousal and orgasm functioning, all of which have been shown to be important in sexual function and satisfaction. With increasing age, there is a decrease in desire, arousal, and orgasm functioning in association with decreasing sexual function.[13,14] It therefore makes sense that younger women, who have increased sexual function and satisfaction, are at a higher risk of a decrease in their sexual function following radiation therapy. Chemotherapy has also been shown to independently decrease sexual arousal and desire, therefore negatively impacting sexual function in a number of ways.[15]

As described above, cervical cancer was not found to be a predictor for decreased sexual function following radiation therapy in our multivariate logistic regression model, despite having a significant association with decreased sexual function in our bivariate analysis. This lack of independent association with decreased sexual function may be explained by cervical cancer's confounding relationships with age and chemotherapy. The cervical cancer population tends to be younger—mean age of diagnosis of 49[16]—and treatment for cervical cancer frequently involves chemotherapy in conjunction with radiation therapy.

Knowing which patient characteristics and treatment factors are predictive of higher risks of decreased sexual function is meaningful because it can help physicians and their gynecologic cancer patients to address concerns of radiation therapy and sexual dysfunction. In multiple studies, physicians and patients have reported that sexual health is rarely discussed when decisions about treatment regimens are being made and risks and benefits of different treatment modalities are being addressed. However, both patients and physicians believe that counseling on sexual health should occur as part of overall cancer care.[17] The results from this study can help to facilitate counseling about sexual health by providing physicians with specific predictors of decreased sexual function following radiation therapy for gynecologic cancer. Physicians will also be able to reassure patients that, when appropriate post-treatment counseling and dilator use occur, the radiation itself, as well as its total dose and location are not associated with decreased sexual function.

Our study compared patients' sexual function prior to and following treatment for gynecologic cancer. This was a strength in our study design because we were measuring a change in sexual function, instead of sexual function at just one point in time. Admittedly, it was also a limitation because we asked patients to remember their sexual function prior to treatment, therefore allowing for recall bias. However, by having patients recall their sexual function prior to treatment and compare it to their current sexual function post-treatment, we were actually gaining access to how these patients perceived their sexual function to change following treatment. This perception of change in sexual function is important data because it provides information about how the patients were feeling about their own sexual health. In other words, in our study, the patients who were found to have decreased sexual function following treatment, personally perceived a negative change in their own sexual function following treatment.

Another strength of our study is our analysis of both IB and EBRT, as all previous studies have only looked at one or the other of these treatment modalities. We were interested in analyzing and comparing these two types of radiation and their associations with decreased sexual function because their utilization in treatment of gynecologic cancers is dramatically skewed. Specifically, IB is significantly underutilized despite substantial evidence that it increases survivorship in gynecologic cancer patients.[18,19] Karabuga et al. found that IB has significantly less impact on QOL in endometrial cancer patients when compared to EBRT, making the underutilization of IB even more concerning.[20] Our study has now also shown that IB and EBRT are associated with similar rates of decreased sexual function, and that both EBRT and IB, individually and as combined treatment, are not risk factors for decreased sexual function. Since it has been proven that IB is an effective and beneficial treatment for gynecologic cancers, and there is now significant evidence that IB does not negatively impact QOL or sexual function, there needs to be more of an effort in the gynecologic oncology and radiation oncology fields to utilize IB whenever appropriate.

We recognize that a main limitation of our study is the sample size. Having a larger sample size would diminish the concern for type II error and allow for more extensive evaluation of factors that do not negatively impact women being treated for gynecologic cancers. Our small sample size also limited our use of a multivariate logistic regression model. We performed this multivariate analysis in order to further assess for true independent associations with decreased sexual function, however our sample of 60 patients makes these results less reliable. A larger study would be beneficial in allowing a larger multivariate analysis to be performed.

6. Conclusions

Our study demonstrated that treatment with EBRT or IB does not appear to impair sexual function in women with gynecologic cancer. Factors that may place women with gynecologic cancer at a higher risk of decreased sexual function following radiation therapy include age less than 50, concurrent chemotherapy, and a diagnosis of cervical cancer. As new cases of gynecologic cancers are presenting each year, it is important that physicians in gynecologic oncology are able to address the long-term effects of various treatments on their patients' survivorship. Understanding the relationship between the treatment modalities and quality of life, physical function and sexual function will help physicians and patients to make more educated decisions on treatment regimens.

Conflict of interest

None declared.

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