Radiation induced bladder dysfunction in women during the acute and chronic phases following pelvic radiotherapy in a prospective observational cohort

Chen Shenhar
Rabin Medical Center, Division of Urology
Bertha H. Chen
Stanford University School of Medicine, Dept. of Obstetrics and Gynecology
Elizabeth A. Kidd
Stanford University School of Medicine, Dept. of Radiation Oncology
Amy D. Dobberfuhl (adobber@stanford.edu)
Stanford University School of Medicine https://orcid.org/0000-0003-3451-3878

Research article

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Abstract

Background

Lower urinary tract symptoms (LUTS) are common after pelvic radiotherapy (XRT), but most existing literature does not account for pre-XRT symptoms. Our aim was to characterize changes in LUTS before, during, and after (acute, chronic) XRT.

Methods

Adult women were prospectively enrolled into an observational cohort over a 10 month period from radiation oncology (Short Term group, ST) and urology (Long Term group, LT) clinic. Instruments included the American Urological Association Symptom Score (AUASS), Female Lower Urinary Tract Symptoms (ICIQ-FLUTS), Short form 12 item health survey, and Radiation Therapy Oncology Group (RTOG) genitourinary toxicity grading system. Data were analyzed in SAS.

Results

Twenty women were recruited (mean age 59.1 ± SD14.8 years, n = 12 ST, n = 8 LT) with a median follow-up of 9 (ST,IQR 7–50) and 6,170 (LT,IQR: 2,194-8,755) days since XRT [brachytherapy (55%,11/20), external beam (15%,3/20), combination (30%,6/20)]. Storage, voiding and incontinence were mildly worse during XRT (not significant). Storage and incontinence LUTS were prevalent before and after XRT. Worse LT scores (vs. ST) were captured by both AUASS and FLUTS for urgency ($p < 0.005$) and frequency ($p < 0.05$). Incontinence was worse in LT and only ascertained by the FLUTS ($p < 0.05$). AUASS quality of life was worse in ST during XRT ($p < 0.05$), and in LT after XRT ($p < 0.05$) when compared to ST. RTOG grade 3–4 toxicity was common (63%,5/8) in the LT group, and not identified at any point during XRT in ST.

Conclusions

XRT is associated with worse LT storage and incontinence, while differences in voiding symptoms did not reach statistical significance.

Background

Radiation induced bladder dysfunction is a common problem after gynecologic oncology radiotherapy. Genitourinary radiation toxicity in the acute phase includes lower urinary tract symptoms (LUTS), urinary urgency, frequency, nocturia, dysuria, bladder spasm, urothelial ulceration and hemorrhage, with an incidence of 20 to 80% depending on dose of radiation [1–3]. Following an asymptomatic latent period, epithelial atrophy, reduction in capacity, loss of compliance and bladder necrosis manifests as a result of progressive vascular damage, obliterative arteritis, ischemia and fibrosis [4]. The Radiation Therapy

Oncology Group (RTOG) has clearly defined genitourinary radiotoxicity using a grading system for acute effects on the lower urinary tract occurring < 90 days after completion of radiotherapy, and late/chronic adverse effects occurring thereafter [5, 6]. Long term urinary adverse events following radiotherapy represent a significant disease burden. Given the close proximity of the cervix and vaginal cuff to the bladder, RTOG grade 1 and 2 urinary adverse events are present in up to 45% of patients at 5-years and major complications related to grade 3 adverse events noted in 14% of patients at 20-years [7–9]. Since the RTOG is the most commonly used radiation toxicity grading system for LUTS in the gynecologic oncology literature [5, 6], it may pose a problem that this score doesn't account for pre-radiation LUTS, which are quite prevalent in the general population, and affect about two-thirds of adult females [10, 11]. The International Continence Society (ICS) terminology classifies LUTS into storage, voiding and post-micturition domains [12], and the International Consultation on Incontinence Questionnaire (ICIQ) further ascertains Female Lower Urinary Tract Symptoms (FLUTS) using the FLUTS questionnaire which classifies both the frequency of the problem and magnitude of bother from each of the ICS storage, voiding and post-micturition domains [13].

Our overarching aims were to (i) prospectively characterize changes in storage and voiding dysfunction during the acute phase of radiotherapy in women treated with radiotherapy for endometrial and cervical cancer; and (ii) systematically quantify the burden of storage and voiding dysfunction in women presenting to a moderate volume urology practice specializing in chronic radiation induced bladder dysfunction.

Methods

This research was performed in accordance with ethical guidelines approved by our Institutional Review Board. Women undergoing (i) pelvic radiotherapy and (ii) presenting to urology clinic with radiation induced bladder complaints signed consent for enrollment into a prospective observational cohort intended to characterize changes in lower urinary tract function before, during and after radiotherapy. Over a 10 month period, women with endometrial and cervical cancer treated with radiotherapy (brachytherapy, external beam, and combination radiotherapy) were enrolled into the short term group (ST) from radiation oncology clinic prior to first radiation exposure. In order to assess long term changes following radiotherapy, women with any history of pelvic radiotherapy presenting for the evaluation of LUTS were enrolled into the long term group (LT) from a moderate volume urology practice specialized in the management of radiation induced bladder dysfunction.

Following enrollment, history was recorded and participants answered self-administered questionnaires which included the American Urological Association Symptom Score (AUASS) [14], the ICIQ-FLUTS [13], and the 12 item short form health survey (SF12) [15]. Radiation Therapy Oncology Group (RTOG) scores [5, 6] were extrapolated from patient notes and symptom questionnaires. To allow comparison of symptoms after radiotherapy with baseline LUTS, in the before radiotherapy phase, an RTOG grade of 0 was assigned for "no/mild LUTS" rather than "no change". Similarly, for the RTOG late/chronic grade assignment, a grade of 0 was assigned for "no/mild LUTS", whereas grade 1 was assigned for mild to moderate frequency and/or urgency, and nocturia more than once per night. Urinalysis variables were scored according to a systematic scale as follows. Leukocyte esterase was assigned 0 for negative result, 1 for trace, and 2–4 for “1+”, “2+”, “3+” respectively. Nitrites were positive or negative. Blood on urinalysis was graded as 0 for negative, 1 for trace, 2 for “1+” or “50”, 3 for “2+” or “250”, and 4 for either “3+” or “full field”.

Primary outcome was change in LUTS before, during and after radiotherapy. Data were analyzed using Statistical Analysis System software (SAS, Cary, NC). Tabulated data are presented as mean ± standard deviation (SD) and number (percentage) of observations. Baseline characteristics were compared using Mann-Whitney-Wilcoxon U text, Fischer’s exact test, and Kruskal-Wallis test. Outcomes were compared using Wilcoxon signed-rank test for paired observations and Kruskal-Wallis test for independent observations. Spearman’s rho was used to test for non-parametric correlations between corresponding questionnaire items. A p-value of $p < 0.05$ was considered statistically significant.

Results

Following IRB approval, twenty women signed consent and were prospectively enrolled over the 10 month study period (May 2019 to February 2020). There were a total of 40 unique patient encounters and 38 questionnaire sets completed (AUASS, ICIQ-FLUTS, SF12). Mean age was 59.1 ± 14.8 years (Table 1). Mean body mass index was 30.1 ± 8.5 kg/m^2. Women previously had a median number of 2 (IQR 0–3) pregnancies and 2 (IQR 0–2) deliveries. Cancer diagnoses were cervical cancer (20%, 4/20), endometrial cancer (65%, 13/20), and other pelvic malignancies (15%, 3/20). Radiotherapy treatments included brachytherapy (55%, 11/20), external beam (15%, 3/20), and combination radiotherapy (30%, 6/20). Prior pelvic surgical treatments included 14 (70%) women treated with radical hysterectomy (with bilateral salpingo-oophorectomy and pelvic lymph node dissection). There were 2 women (10%) who were pre-menopausal, and the remaining 18 women were post-menopausal at time of radiotherapy.

Table 1
Patient characteristics grouped by longest follow-up after radiotherapy

	Radiation group by follow-up			
	Overall (n = 20)	Short term (n = 12)	Long term (n = 8)	p-value
Demographics				
Age (years, mean ± SD)	59.1 ± 14.8	61.8 ± 14.1	55.0 ± 15.9	0.30*
BMI (kg/m^2, mean ± SD)	30.1 ± 8.5	31.1 ± 10.2	28.6 ± 5.3	0.73*
History of pregnancy				
Gravity (#, median, IQR)	2 (0–3)	1 (1–2)	2 (0–4)	0.63*
Parity (#, median, IQR)	2 (0–2)	2 (0–2)	2 (0–3)	0.61*
Menopause status				
Premenopause (n, %)	2 (10%)	1 (8.3%)	1 (12.5%)	0.54
Postmenopause (n, %)	18 (90%)	11 (91.7%)	7 (87.5%)	
Primary malignancy				
Cervical (n, %)	4 (20%)	2 (16.7%)	2 (25%)	0.051
Endometrial (n, %)	13 (65%)	10 (83.3%)	3 (37.5%)	
Other (n, %)	3 (15%)	-	3 (37.5%)	
Pelvic surgery				
Hysterectomy (n, %)	14 (70%)	10 (83.3%)	4 (50%)	0.014
Other (n, %)	4 (20%)	-	4 (50%)	
None (n, %)	2 (10%)	2 (16.7%)	-	
Radiotherapy				
Brachytherapy (n, %)	11 (55%)	9 (75%)	2 (25%)	0.041
External beam (n, %)	3 (15%)	-	3 (37.5%)	
Combination (n, %)	6 (30%)	3 (25%)	3 (37.5%)	
Follow-up				
Time since last XRT (days, median, IQR)	72 (7 – 4,513)	9 (7–50)	6,170 (2,194-8,755)	0.0001*

BMI body mass index, *IQR* interquartile range, *SD* standard deviation, *XRT* radiotherapy

Radiation group by follow-up
(*) Mann-Whitney-Wilcoxon U test, (□) Fischer’s exact, (□) Kruskal Wallis
BMI body mass index, *IQR* interquartile range, *SD* standard deviation, *XRT* radiotherapy

Median follow-up time since last radiotherapy treatment was 77 days (IQR 7 – 4,513) days for the whole group (Table 1). Subjects in the ST group recruited before commencing radiotherapy had a median follow-up of 9 (IQR: 7–50) days since radiotherapy, while patients recruited from urology clinic in the LT follow-up group had a median interval of 6,170 (IQR 2,194-8,755) days since radiotherapy. The ST and LT groups differed in the types of cancer, pelvic surgeries performed and radiotherapy. There were no differences in mean age, gravity, parity, BMI, or menopause status.

For the LUTS storage domains (daytime frequency, urinary urgency, nocturia), there were differences in the magnitude of change over time when correlating the AUASS against the ICIQ-FLUTS (Table 2). Daytime frequency (AUASS #2 vs. FLUTS #5) was decreased by 1 to 2 AUASS points in approximately 50% of the women during brachytherapy, meanwhile FLUTS score increased in most patients over time (Spearman $r = 0.443$, $p = 0.005$, Fig. 1). Similarly for the urgency domain (AUASS #4 vs. FLUTS #3) AUA scores had dramatic 2 to 4 point changes in all directions, while FLUTS scores were more consistently changed across patient groups, and were worse after combination radiotherapy (Spearman $r = 0.700$, $p < 0.001$, Fig. 1). For the nocturia domain (AUASS #7 vs. FLUTS #2) there were high baseline AUA scores in the brachytherapy group, where some women reported paradoxical improvement in AUASS LUTS, and some worsened following radiotherapy. Meanwhile for the assessment of nocturia, the FLUTS scores appeared more consistent over time (Spearman $r = 0.832$, $p < 0.001$, Fig. 1). Generally, women undergoing combination radiotherapy had worse or unchanged nocturia during treatment, and following radiotherapy there was consistently greater nocturia reflected in both the AUASS and FLUTS.

Table 2
Subjective and objective effects on lower urinary tract stratified by time since radiotherapy

	Short term			**Long term**
	Before XRT (n = 12)	During XRT (n = 11)	After XRT (n = 4)	After XRT (n = 8)
AUASS questionnaire (mean ± SD)				
1. Incomplete emptying	0.7 ± 1.4	0.6 ± 0.9	0.5 ± 0.5	2.6 ± 2.2
2. Frequency	1.5 ± 1.7	1.0 ± 1.2	0.7 ± 0.9	4.0 ± 1.4*
3. Intermittency	1.1 ± 1.6	1.0 ± 1.5	1.0 ± 2.0	2.7 ± 2.3
4. Urgency	1.5 ± 1.8	1.8 ± 2.0	1.0 ± 1.1	4.3 ± 0.9**
5. Weak stream	1.1 ± 1.7	0.8 ± 1.4	1.0 ± 1.1	2.2 ± 2.0
6. Straining	0.6 ± 1.4	0.3 ± 0.9	0.5 ± 1.0	2 ± 2.1.0
7. Nocturia	1.8 ± 1.0	2.2 ± 1.2	2.2 ± 0.9	3.1 ± 1.7
Total AUA symptom score	8.5 ± 9.4	8.0 ± 6.0	7.0 ± 4.2	21.2 ± 10.9*
Quality of life	1.1 ± 1.1	2.0 ± 1.5*	1.5 ± 1.2	4.0 ± 1.1*
FLUTS questionnaire (mean ± SD)				
2. Nocturia	1.7 ± 1.0	1.7 ± 0.7	2.0 ± 0.8	2.8 ± 1.3
3. Urgency	1.0 ± 1.0	1.4 ± 1.1	1.0 ± 1.1	2.5 ± 1.0*
4. Pain	0.0 ± 0.0	0.2 ± 0.6	0.2 ± 0.5	1.9 ± 1.8
5. Micturition frequency	0.1 ± 0.3	0.2 ± 0.4	0.0 ± 0.0	2.6 ± 1.7*
6. Hesitancy	0.2 ± 0.4	0.2 ± 0.4	0.5 ± 0.5	1.0 ± 1.2
7. Straining	0.1 ± 0.3	0.3 ± 0.9	0.0 ± 0.0	1.6 ± 1.6
8. Intermittency	0.7 ± 0.9	0.7 ± 0.9	0.5 ± 0.5	1.9 ± 1.6
9. Urge Incontinence	1.0 ± 1.2	1.0 ± 1.3	1.0 ± 1.1	2.2 ± 1.3
10. Incontinence frequency	1.2 ± 1.6	1.1 ± 1.3	1.0 ± 1.4	3.1 ± 1.1*
11. Stress Incontinence	0.9 ± 1.1	1.0 ± 1.0	0.2 ± 0.5	1.4 ± 1.6
12. Unawareness incontinence	0.2 ± 0.4	0.1 ± 0.4	0.2 ± 0.5	1.2 ± 1.5

AUASS American Urological Association Symptom Score, *FLUTS* Female Lower Urinary Tract Symptoms, *GU* genitourinary, *RTOG* Radiation Therapy Oncology Group, *SD* standard deviation, *SF12* Short form 12 item health survey, *XRT* radiotherapy

	Short term			Long term
13. Nocturnal enuresis	0.1 ± 0.5	0.3 ± 0.6	0.5 ± 1.0	1.6 ± 1.6
SF12 questionnaire (mean ± SD)				
Overall health (1–5, poor - excellent)	2.5 ± 1.0	2.6 ± 0.9	2.0 ± 0.8	3.5 ± 1.1*
Urinalysis (mean ± SD)				
Leukocyte esterase (0–4, none – 3+)	0.2 ± 0.6	0.2 ± 0.6	0.5 ± 1.0	1.3 ± 1.4
Nitrite (0–1, none - positive)	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.3 ± 1.5
Blood (0–3, none – 3+)	0.3 ± 0.9	0.0 ± 0.0	0.0 ± 0.0	1.3 ± 1.2*
RTOG GU toxicity (acute, < 90 days)				
RTOG grade (mean ± SD)	0.6 ± 0.7	1.1 ± 0.7	1.3 ± 0.5	n/a
RTOG grade 1–2 (n, %)	6/12 (50%)	9/11 (82%)	4/4 (100%)	n/a
RTOG grade 3–4 (n, %)	-	-	-	n/a
RTOG GU toxicity (late/chronic)				
RTOG grade (mean ± SD)	n/a	n/a	n/a	2.5 ± 0.7*β
RTOG grade 1–2 (n, %)	n/a	n/a	n/a	3/8 (37%)
RTOG grade 3–4 (n, %)	n/a	n/a	n/a	5/8 (63%)

(*) $p < 0.05$, (**) $p < 0.005$, (β) acute versus late/chronic

AUASS American Urological Association Symptom Score, *FLUTS* Female Lower Urinary Tract Symptoms, *GU* genitourinary, *RTOG* Radiation Therapy Oncology Group, *SD* standard deviation, *SF12* Short form 12 item health survey, *XRT* radiotherapy

For the LUTS voiding domains (weak stream, urinary hesitancy, straining, intermittency), there were differences in the magnitude of change over time when contrasting the AUASS against the FLUTS (Table 2). Urinary hesitancy (FLUTS #6) was not a common problem during brachytherapy in the ST group, however was common in the LT group after external beam and combination radiotherapy, although this may reflect a referral pattern for the LT group. Similarly, straining was not a common problem during brachytherapy, as reflected by FLUTS scores, but was more pronounced during and after external beam and combination radiotherapy. Straining to void scores (AUASS #6 vs. FLUTS #7) were closely correlated (Spearman r = 0.753, $p < 0.001$, Fig. 1). Intermittent urinary stream scores (AUASS #3 vs. FLTUS #8) were closely correlated (Spearman r = 0.827, $p < 0.001$, Fig. 1). Intermittency fluctuated over the acute time course, with the brachytherapy group having fairly high baseline AUA scores which seemed to improve during/after radiotherapy, meanwhile FLUTS scores did not show this trend through the course of radiotherapy. Women undergoing combination radiotherapy had higher AUA scores, but only a mild increase in FLUTS scores during radiotherapy. Meanwhile in the LT group after external beam radiotherapy, there were consistently higher scores in both the AUASS and FLUTS.

For the LUTS incontinence domains (Table 2), women had relatively high incontinence scores at baseline (FLUTS #9–12). There were paradoxical changes in incontinence score during/after brachytherapy, discordant with expected pathophysiology of radiation, which has been classically associated with exacerbation of storage symptoms. Combination treatment was associated with increased or no change in incontinence during radiotherapy, meanwhile in the LT group after external beam and combination radiotherapy, women usually had high incontinence scores, although this may reflect a referral pattern to a moderate volume urology practice specialized in the management of radiation induced bladder dysfunction. Bladder pain (FLUTS #4) was temporarily increased during brachytherapy and combination radiotherapy, whereas on long-term follow-up bladder pain was much greater in each of these groups. For the overall and quality of life domains, perception of overall health (SF12) was reported as “good” or “very good” by most brachytherapy patients, with no clear trend during treatment, and improvement after radiotherapy ended. On correlation analysis, external beam and combination radiotherapy women had generally worse perception of overall health (SF12) and AUASS quality of life, and overall for all groups scores between these domains were moderately correlated (AUASS quality of life vs. SF12 overall health, Spearman $r = 0.450$, $p = 0.005$, Fig. 1). For the rest of the questions on the SF12 questionnaire, there were no significant differences in SF12 questions among subjects before, during and after radiotherapy in the ST group, or in the LT follow up group. Patients in the LT follow-up group had worse scores for questions asking about pain interfering with normal work (#8), feeling clam and peaceful (#9) and having energy (#10), but these differences did not reach statistical significance.

Urinalysis results were mostly normal before, during and after radiotherapy in the ST group (Table 2), with different and abnormal/elevated results mostly in the LT group after radiotherapy, reaching statistical significance only for blood on urinalysis ($p = 0.037$). RTOG scores were minimally and insignificantly elevated during and after radiotherapy, with no patient experiencing any grade 3 or 4 toxicity in the ST group (Table 2). In the LT group, RTOG scores were significantly worse, when compared to the ST post-radiotherapy acute RTOG scores, with 5 of 8 (63%) women found to have grade 3 toxicity on 1 or more follow-up visits, although this may reflect a referral pattern for the LT group.

Discussion

In women who underwent brachytherapy and combination radiotherapy, the FLUTS storage and voiding domains scores were more consistent than the AUASS with respect to the expected pathophysiology of radiation induced bladder dysfunction after taking into account magnitude and direction of change in symptoms over the time course of radiotherapy. Incontinence was prevalent at baseline, during and after radiotherapy. Pain was mostly a problem for external beam and combination radiotherapy. Perception of overall health was generally better with brachytherapy than in external beam and combination radiotherapy groups. Paradoxical changes in AUASS and FLUTS were observed over the course of radiotherapy which warrants further clinical discussion and the clinician in these circumstances should seek clarification in women regarding changes in LUTS before, during and after radiotherapy. Blood on urinalysis was more common among the LT follow-up group, as were worse RTOG grades, although the late/chronic RTOG grades were not directly comparable to acute grades given the slight differences in the acute versus late/chronic RTOG grading system.

Upon review of the literature, we found three published studies that have described acute phase radiation associated LUTS, in women with cervical and endometrial cancer. The PORTEC-2 trial, which randomized 427 women to either external beam or vaginal brachytherapy, found a sharp, transient increase in urinary urgency immediately after radiotherapy in the external beam but not in the brachytherapy radiation treatment group [16]. The NRG oncology-RTOG 1203 trial of 278 women, found deterioration in LUTS as measured by the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, with gradually worsening symptoms during radiotherapy in all domains (function, bother, incontinence, irritation/obstruction), and then improvement at the 4 to 6 week post radiotherapy time point [17]. Roszak et al. found a rate of 21 to 26% overall bladder toxicity and 3 to 8% RTOG grade 3 to 4 toxicity during radiotherapy, in a study of 225 female patients receiving pelvic radiotherapy [18]. In our study, we found that 50% of patients reported some degree of pre-treatment LUTS, and 82% reported bothersome LUTS during treatment. Many of these would not be captured by the RTOG score which requires a two-fold exacerbation from pre-treatment habit to be considered grade 1 toxicity.

With regards to long-term follow up, we found six publications that reported long-term LUTS after radiotherapy. The PORTEC-2 trial [16] continued follow-up for up to 7 and 10 years on 202 and 80 patients, respectively. Long-term follow up has shown a significant increase over time in nocturia, urgency, incontinence, and limitation in daily activities due to LUTS. Dysuria complaints were found to decrease over time, unlike our study in which all domains including bladder pain were worse in the LT group of patients at follow-up (Table 2). Overall in the PORTEC-2 trial, external beam resulted in worse LUTS than brachytherapy, which is in concordance with the findings of our study. Roszak et al. has also published late bladder toxicity data, where after a 2 year follow-up interval after radiotherapy, an overall bladder toxicity rate of 2 to 6% was found, of which none were RTOG grade 3 or more [18]. The RetroEMBRACE study on 731 patients also used RTOG score and identified a rate of 4% grade 3 + genitourinary toxicity at 3 years of follow up and 5% at 5 years [19]. Meanwhile Keys et al. found no grade 3 or more bladder toxicity in 190 patients receiving external beam radiotherapy after a mean follow up of 5.8 years, whereas in their series 30% had RTOG grade 1 to 2 toxicity, versus 8% of patients who underwent surgery alone ($p < 0.001$) [20]. In our study, patients presenting with long-term LUTS after pelvic radiotherapy had a rate of 63% grade 3 to 4 toxicity, which is more representative of a patient population seeking care for their radiation induced LUTS. This is likely because our institution is a referral center for women in the LT group, and therefore enriched for this type of patient, while the PORTEC-2 study included a greater proportion of long term follow-up on all initially enrolled participants.

Emirdar et al [21] have performed urodynamic studies and physical examination for incontinence and compared patient status both before, and 6 months after radiotherapy. Bladder capacity was decreased significantly in all subjects, and mostly in those undergoing radical pelvic surgery in combination with the lowest dose of radiation (mean decrease in capacity from 600 to 490 mL). Stress incontinence rates increased from 28–39% in the radical surgery group, and from 40–70% in the abdominal hysterectomy and radiotherapy group. Definitive radiotherapy patients had no stress incontinence before or after treatment. In our study mean scores for all FLUTS and AUASS questions were worse for the LT follow up group, while only frequency, urgency, incontinence and quality of life reached statistical significance, perhaps due to being underpowered.

Katepratoom et al. [22] utilized LUTS questionnaires and urodynamic pressure-flow evaluation to compare radical hysterectomy (n = 35) against combination radiotherapy (n = 35). After a mean follow-up of 5.7 years, overall LUTS were insignificantly different, 60% in the radiotherapy and 69% in the surgery group, which is not very different from the general female population [10, 11] and no significant differences for urinary incontinence were identified. Voiding dysfunction was worse in the patients treated with surgery, while storage symptoms were more prevalent in the radiotherapy group. Finally, Bregendahl et al. [23] looked at 516 females undergoing surgery for rectal cancer, out of which 154 received neoadjuvant radiotherapy. Patients completed FLUT questionnaires; however they failed to capture pre-treatment LUTS prior to radiotherapy. From this study the authors found that pre-operative radiotherapy was a risk factor for voiding complaints (OR 1.63, 95% CI 1.09–2.44), but not for storage or incontinence problems. In our present investigation which focused on female pelvic malignancies, in the LT group we found significantly worse FLUTS and AUASS scores for most storage LUTS and some incontinence, while differences in voiding symptoms did not reach statistical significance (Table 2).

The strengths of our present study are the prospective observational cohort study design, granularity of all patients completing the same set of questionnaires over consecutive time points for women in the ST group, and the reliability achieved by patients reporting symptoms blinded to their previous questionnaire answers. Since pelvic radiotherapy in women is relatively uncommon when compared to prostate cancer radiotherapy in men, we present a relatively high volume of cases recruited over a short time period of just 10 months, utilizing ICS terminology and concepts, and including pre-radiation LUTS. Our study limitations include the small sample size, patient heterogeneity due to relative paucity/rarity of radiotherapy in women, and patient recollection of their self-reported LUTS. Additionally, given that there was not a urology consultation required in the ST group prior to radiotherapy, potential for selection bias exists as women with more severe LUTS may have self selected to not undergo radiotherapy in our series. Such patients might have underlying LUTS which would be exacerbated by radiotherapy, and lead to a serious deterioration in quality of life, making them poor candidates for radiotherapy. We recommend that women with significant LUTS prior to radiotherapy undergo urology consultation to include a more comprehensive discussion of LUTS, clinical history and urologic pelvic exam prior to radiotherapy. Additional considerations which need to be made before generalizing the findings of our study include the lack of pre-radiotherapy LUTS for women in the LT follow-up group, and the incomplete reporting of post-radiotherapy LUTS in the after radiotherapy ST group due to the short recruitment interval of our 10 month study. Additionally, our small sample size limits study power to demonstrate small differences in LUTS or quality of life, which could become statistically significant as we continue to recruit more women to our cohort. However, as a tertiary care referral center for radiotherapy, our numbers are large for this relatively rare treatment for a single study site. Taking these limitations into account, our study emphasizes the importance of baseline LUTS assessment prior to radiotherapy.

Conclusions

Classically radiotherapy has been associated with urinary urgency, frequency and worsening incontinence, which appear to be better captured by the FLUTS questionnaire due to the inclusion of incontinence domain questions. In our present investigation, we found significantly worse FLUTS and AUASS scores for most storage LUTS and some incontinence in the LT group, while differences in voiding symptoms did not reach statistical significance.

Abbreviations

AUASS American Urological Association Symptom Score questionnaire

BMI Body mass index

FLUTS Female Lower Urinary Tract Symptoms questionnaire

ICIQ International Consultation on Incontinence

ICS International Continence Society

IQR Interquartile range

LUTS Lower urinary tract symptoms

LT Long term follow-up group

RTOG Radiation Therapy Oncology Group

SD Standard deviation

SAS Statistical Analysis System software

SD Standard deviation

SF12 Short form 12 item health survey questionnaire

ST Short term follow-up group

XRT Radiotherapy

Declarations

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Conflicts of Interest:

The authors declare that they have no conflicts of interest in relation to the content of the manuscript.

Ethics approval:

This research was performed in accordance with ethical guidelines approved by the Stanford University Institutional Review Board (IRB Protocol # 45362)

Consent to participate

All subjects signed informed consent to participate in this prospective observational cohort.

Availability of data and materials:

The data that support the findings of this study were obtained from the Stanford University School of Medicine electronic medical record, and are not publicly available. De-identified data are available from the authors upon reasonable request and with permission of the Stanford University IRB.

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Figures

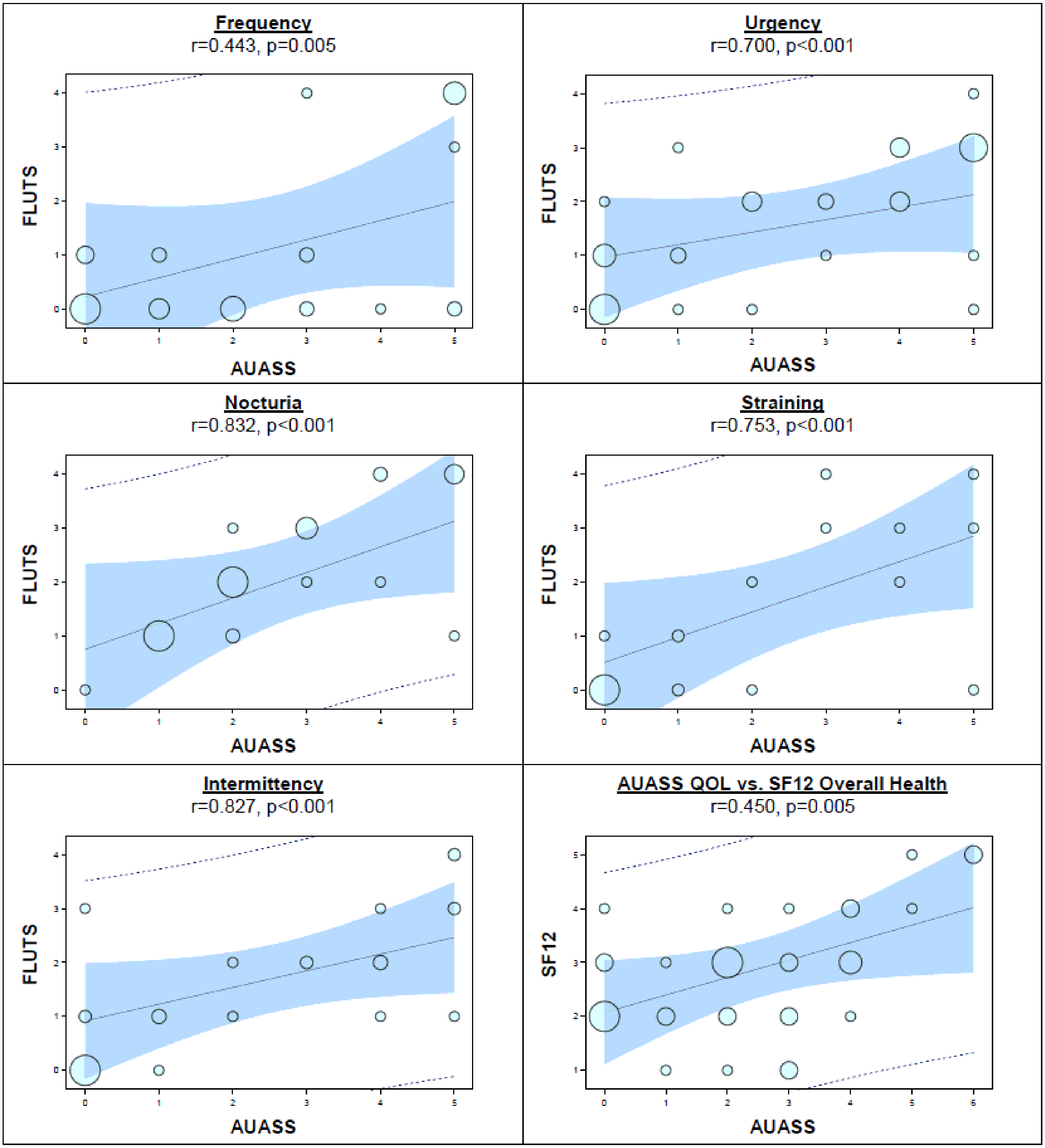

Figure 1

Spearman correlation between AUASS, FLUTS and SF12 questionnaires. AUASS American Urological Association Symptom Score, FLUTS Female Lower Urinary Tract Symptoms, SF12 Short form 12 item health survey