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Journal Title: Gynecologic Oncology

Volume: Volume 154, Number 1

Publisher: Academic Press Inc. Elsevier Science | 2019-07-01, Pages 183-188

Type of Work: Article | Post-print: After Peer Review

Publisher DOI: 10.1016/j.ygyno.2019.04.682

Permanent URL: https://pid.emory.edu/ark:/25593/vnw38

Final published version: http://dx.doi.org/10.1016/j.ygyno.2019.04.682

Copyright information:

HHS Public Access

Author manuscript

Gynecol Oncol. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Gynecol Oncol. 2019 July ; 154(1): 183–188. doi:10.1016/j.ygyno.2019.04.682.

Expanded Validation of the EPIC Bowel and Urinary Domains for Use in Women with Gynecologic Cancer Undergoing Postoperative Radiotherapy

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Abstract

Objective: Women with endometrial or cervical cancer at risk for recurrence receive postoperative radiation therapy (RT). A patient reported outcomes (PRO) instrument to assess bowel and urinary toxicities is the Expanded Prostate Cancer Index Composite (EPIC), which has been validated in men with prostate cancer. As this instrument specifically measures bowel toxicity and the degree to which this is a problem, it was used in NRG Oncology/RTOG 1203 to compare intensity modulated RT (IMRT) to standard RT. This paper reports on the expanded validation of EPIC for use in women receiving pelvic RT.

Methods: In addition to the EPIC bowel domain, urinary toxicity (EPIC urinary domain), patient reported bowel toxicities (PRO-CTCAE) and quality of life (Functional Assessment of Cancer Therapy (FACT)) were completed before, during and after treatment. Sensitivity, reliability and concurrent validity were assessed.

Results: Mean bowel and urinary scores among 278 women enrolled were significantly worse during treatment and differed between groups. Acceptable to good reliability for bowel and urinary domain scores were obtained at all time points with the exception of one at baseline. Correlations between function and bother scores within the bowel and urinary domains were consistently stronger than those across domains. Correlations between bowel domain scores and PRO-CTCAE during treatment were stronger than those with the FACT.

Conclusion: Correlations within and among the instruments indicate EPIC bowel and urinary domains are measuring conceptually discrete components of health. These EPIC domains are valid, reliable and sensitive instruments to measure PRO among women undergoing pelvic radiation.

Keywords

Bowel and urinary toxicity; pelvic radiation; cervical and endometrial cancer; patient reported outcomes

1. Introduction

Women treated with hysterectomy for endometrial or cervical cancer with risk factors for recurrence receive radiation therapy (RT), with or without chemotherapy [1 – 6]. Radiation therapy (RT) to the pelvis is associated with toxicities including diarrhea, pain, bleeding, fecal and urinary incontinence [7 – 8]. These toxicities are burdensome to patients, interfere with quality of life and can lead to interruptions in treatment [9]. Accurate assessment of

toxicities is important as modification to therapies are introduced and as potential interventions to reduce acute gastrointestinal (GI) and urological symptoms are tested [9]. Assessment of toxicities can be accomplished by clinicians, but clinicians often under report toxicities [10] and including patient reported outcomes (PRO) provides a clearer understanding of how the treatment is tolerated [11]. A PRO instrument that specifically addresses bowel and urinary toxicities associated with radiation to the pelvis and includes assessment of the degree to which these toxicities are a problem is the Expanded Prostate Cancer Index Composite which has been validated in men receiving treatment for prostate cancer (EPIC) [12]. This instrument is well suited for accurately determining the clinically meaningful impact of differences in bowel irradiation on acute toxicity across treatment groups.

This instrument was used in a recent assessment of intensity-modulated radiation therapy (IMRT), a method of radiotherapy delivery that allows for conforming the dose to the shape of the target, thereby reducing the dose to adjacent normal tissues, versus traditional four field RT in women treated with hysterectomy for endometrial or cervical cancer (RTOG1203) [13]. These women were randomized to receive IMRT or standard RT; the primary endpoint was change in acute GI toxicity at the end of RT (five weeks) measured with the bowel domain of EPIC [12]. The bowel domain of EPIC sums severity of symptoms and bother resulting from those symptoms, with higher scores indicating better quality of life; mean EPIC bowel summary scores decreased significantly less in the IMRT group [13].

The urinary domain of EPIC was also included in RTOG 1203 study to examine the impact of the two treatment regimens on urinary toxicity. The EPIC urinary module measures frequency of leaking urine, urination of blood, pain and loss of urinary control as well as the extent to which each of these symptoms is a problem. Mean EPIC urinary summary scores decreased significantly less in the IMRT group [13].

Additional PRO measured in RTOG 1203 were quality of life (QOL) using the Functional Assessment of Cancer Therapy-Cervix (FACT-Cx) and the NCI Patient Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE). The FACT-Cx is a validated instrument that measures physical, functional, emotional and social well-being, as well as additional concerns related to cervical cancer [14–16]. The PRO-CTCAE is used to assess severity of treatment toxicity and extent to which these toxicities interfere with daily activities directly from the patient [17 – 18]. In RTOG 1203, PRO-CTCAE items including abdominal pain, and specific bowel problems were used to assess toxicities. As multiple PRO instruments were used, an in depth, protocol-specified, validation of the EPIC bowel and urinary domains for use in RT of the pelvis for women is reported here, as has previously been reported for men treated for prostate cancer [12].

2. Methods

2.1 Participants and design

NRG Oncology's RTOG 1203 was funded by the National Cancer Institute and is registered in clinicaltrials.gov (). Women were enrolled into the study after providing written informed consent from 88 institutions in three countries following IRB approval at each institution.

Patients with cervical or endometrial cancer with indications for postoperative RT after hysterectomy were randomized 1:1 to receive either standard 4-field pelvic RT or pelvic IMRT. Patients were treated to 45 Gy or 50.4 Gy based on physician preference. Five cycles of weekly cisplatin 40 mg/m^2 were given at the physician's discretion according to predefined pathologic criteria. Patients were stratified by dose (45 vs. 50.4 Gy), use of chemotherapy (yes vs. no), and disease site (cervix vs. endometrium). Patients were excluded if they were unable to fill their bladder, required extended-field RT, had a history of inflammatory bowel disease, had evidence of active infection, or had previously received RT.

2.2 Assessments

An expanded validation of the EPIC bowel and urinary domains in this setting was a pre-specified secondary endpoint of the randomized trial. Multiple instruments exist for measuring toxicity resulting from pelvic radiation and impact on quality of life [19,20]. The following were selected as they assessed clinically meaningful impact of differences in bowel irradiation on acute GI toxicity across treatment groups. Patients completed the EPIC bowel and urinary domains, the FACT-Cx, and the six PRO-CTCAE items. These instruments were completed before treatment, after 13 to 15 fractions (3 weeks), after 23 to 25 fractions (5 weeks), and 4 – 6 weeks after completion of RT except to minimize the survey burden for patients, evaluations at 3 weeks of treatment included only the EPIC.

The EPIC is a PRO instrument designed to evaluate bowel, urinary, sexual and hormonal domains both during and after irradiation of the pelvis. Only two of the four domains, bowel and urinary, were used in this study, and the frame of reference was modified to "the last 7 days" with permission from the copyright holder. The EPIC bowel domain consists of 14 items, 7 assessing the severity of symptoms and 7 assessing the extent to which each symptom bothers the patient. The EPIC urinary domain consists of 12 items, 5 assessing the severity of symptoms and 7 assessing the extent to which symptoms bother the patient. The EPIC urinary domain incontinence subscale consists of 4 items from the EPIC urinary domain, and the EPIC urinary domain irritation/obstruction subscale consists of 7 items from the EPIC urinary domain. One item from the EPIC urinary domain is not included in the incontinence or irritation/obstruction subscales. For each domain, responses are provided on a 5-point Likert scale, and multi-item scale scores are transformed linearly to a scale of 0 to 100, where higher scores correspond to better quality of life. At least 80% of the items in a domain or subscale of the domain must be completed in order to compute the score.

The FACT-Cx consists of the FACT-General, a validated, 27-item measure of QOL in patients with cancer divided into the four subscales of physical, functional, social, and emotional well-being, and an additional subscale of cervix specific concerns [14]. The additional cervix specific concerns subscale is a 15-item assessment that was developed for patients with cervical cancer [15]. These additional concerns include questions about sex, appetite, and urination. There are no questions concerning diarrhea. Since patients with cervical and endometrial cancer were treated the same way and no differences between cervical and endometrial cancer patients in functioning due to treatment were expected, it was felt that the FACT-Cx would provide valuable information not only for patients with

cervical cancer but also for patients with endometrial cancer. The Trial Outcome Index (TOI) is a composite score of physical and functional well-being and additional concerns from the FACT-Cx that are directly impacted by disease and treatment [10]. For a subscale of the FACT-Cx to be scored, at least 50% of the items must be completed.

The PRO-CTCAE was developed to characterize, from the patient's perspective, the frequency and severity of treatment toxicities and the extent to which these toxicities interfere with daily activities [17]. Responses were provided on a 5-point Likert scale (0=none to 4=very severe), and the recall period was the past 7 days. Each item is analyzed separately. For this study, three adverse events related to pain in the abdomen (severity and interference), loose or watery stools (frequency), and loss of bowel movement control (frequency and interference) were used. Patients were also asked how many antidiarrheal medications were taken on average over the past 7 days.

2.3 Statistical Analysis

NRG Oncology statisticians performed the study analysis using SAS ® Version 9.4 of the SAS System for Windows. The sensitivity of the EPIC bowel and urinary domains to treatment was examined with a linear effects model over time (baseline, 3 weeks, 5 weeks and 4 – 6 weeks post-treatment). To measure internal consistency reliability, Cronbach's alpha was calculated for the urinary and bowel subscales at each time point. Acceptable reliability was considered an alpha of 0.6 – 0.7 while good reliability was indicated with alpha of 0.8. The correlation between function and bother within the urinary and bowel domains were calculated along with pairwise Spearman correlation coefficients for all of the items in the bowel and urinary domains to assess conceptual independence. The urinary and bowel domains of the EPIC were correlated with the FACT-G, TOI, and PRO-CTCAE to determine concurrent validity at baseline, 5 weeks and 4 – 6 weeks.

3. Results

3.1 Patients and Impact of Treatment

There were 278 eligible women who enrolled into RTOG 1203 (Table 1). The EPIC was completed by 99.3% of patients at baseline, 88.1% at week 3 of RT, 86.7% at week 5 of RT, and 81.6% at 4 to 6 weeks after RT with compliance rates similar between the treatment groups at each time point. There were no significant differences between the two treatment groups in pretreatment characteristics (Table 1). As previously reported, mean bowel and urinary summary scores were worse at week 3 of treatment, declined further by week 5 and improved by 4 – 6 weeks of treatment; a linear effects model demonstrated a significant effect of time for both domains [13]. Complete results from this study have been published [13].

3.2 Cronbach's Alpha for EPIC Bowel and Urinary Domain Scores

Acceptable to good reliability was obtained for bowel and urinary domain scores at all time points except bowel function at baseline (Table 2). Cronbach's alpha was 0.77 for the bowel summary scores at baseline and increased to 0.89 during (at 3 and 5 weeks) and after treatment (at 4 – 6 weeks post treatment). Less than acceptable reliability at baseline was

obtained for bowel function scores (0.48) but reliability for this measure increased to 0.70 – 0.72 at the later time points. Cronbach's alpha score was 0.84 for the urinary summary scores at baseline and increased to 0.87 – 0.89 at the later time points.

Cronbach's alpha at each time point were run within patients who did not receive chemotherapy (n=207) and those who did (n=71). The results were similar between these two groups for Cronbach's alpha (data provided in Supplemental Table S1).

3.3 Correlations between EPIC Bowel and Urinary Domain Scores

Correlations between function and bother scores within a domain were consistently stronger than correlations across domains at all time points (Table 3). Correlations between bowel function and bother scores ranged from 0.63 at baseline to 0.81 at 3 and 5 weeks. Correlations between the urinary function and bother scores ranged from 0.67 – 0.75. Correlations between bowel and urinary domains ranged from 0.23 – 0.56.

The correlations between the bother and function scores in women who did not and did receive chemotherapy were also calculated. Although there were minor differences in correlations between the two groups, correlations between function and bother scores within a domain were consistently stronger than correlations across domains at all time points for both groups (data provided in Supplemental Table S2).

3.4 Correlations between EPIC Domains and FACT

Correlations between EPIC bowel and urinary summary scores and FACT-G ranged from 0.39 – 0.44 (Table 4). Correlations between EPIC bowel and urinary summary scores and FACT-TOI were slightly stronger, ranging from 0.47 – 0.54 (Table 5).

3.5 Correlations between EPIC Domains and PRO-CTCAE

Correlations between patient reported pain in the abdomen (severity and interference) and the summary EPIC bowel scores ranged from −0.47 to −0.62 over all time points and were stronger than correlations between these questions and summary urinary scores which ranged from −0.20 to −0.44 (Table 6). Correlations between patient reported frequency of loose or watery stools and the summary EPIC bowel scores increased from −0.37 at baseline to −0.79 at 5 weeks (Table 6). As expected, correlations between this question and EPIC bowel summary scores were stronger than those with EPIC urinary summary scores which increased from −0.14 to −0.31 (Table 6). Correlations between patient-reported frequency of loss of bowel movement control and the summary EPIC bowel scores increased from −0.28 at baseline to −0.49 at 5 weeks (Table 6). Correlations between this question and EPIC bowel summary scores were stronger than those with EPIC urinary summary scores (Table 6).

4. Discussion

The EPIC bowel and urinary domains were demonstrated to be valid, reliable and sensitive instruments for use in assessing bowel and urinary toxicity severity and impact in women undergoing pelvic radiation following hysterectomy. Both domains were sensitive to the

effect of treatment over time. Cronbach's bowel alpha scores were greater than 0.70 for all time points save bowel function at baseline. In regards to the single score at baseline, there are no comparison data from the validation study in men, as that study did not include time points prior to treatment [12]. It may be that EPIC is not acceptably valid in cancer patients who have yet to undergo treatment. Cronbach's alpha for bowel summary, function and bother scores in this study at 5 weeks were very similar to those obtained in the validity study of men with prostate cancer who underwent treatment [12] (bowel summary 0.89 vs 0.92; function 0.71 vs 0.75; bother 0.88 vs 0.90, respectively). Cronbach's alpha for urinary summary, function, bother, irritation and incontinence scores in this study at 5 weeks were very similar to those obtained in the validity study of men with prostate cancer who underwent treatment [12] (urinary summary 0.89 vs 0.88; function 0.73 vs 0.69; bother 0.86 vs 0.85, irritation 0.79 vs 0.81 and incontinence 0.92 vs 0.89, respectively).

Correlations between function and bother scores within the bowel and urinary domains were stronger than those with scores from the other domain (Table 3) suggesting the bowel and urinary domains are measuring conceptually discrete components of health. Correlations between the bowel function and bother scores at 5 weeks were also similar to those obtained in the validity study of men with prostate cancer (0.81 vs 0.87, respectively), as were urinary function and bother scores (0.74 vs 0.69, respectively) [12].

The correlations between bowel summary scores and PRO-CTCAE questions concerning pain in the abdomen, frequency of loose or water stools and frequency of loss of bowel movement control at 5 weeks ranged from −0.49 to −0.79 and were stronger than those between urinary summary scores and the PRO-CTCAE questions (−0.26 to −0.44), again demonstrating the bowel domain was measuring a different component of health from that which was measured in the urinary domain. The correlations at 5 weeks between the bowel summary scores and PRO-CTCAE questions concerning pain in the abdomen and frequency of loose stools (−0.62 and −0.79, respectively) were also stronger than those between the bowel summary scores and the FACT-G or FACT-TOI (0.44 and 0.53, respectively). This again suggests the EPIC bowel domain is measuring different aspects of the effect of radiation treatment. The correlation between the bowel and urinary summary scores and the FACT-G and TOI were similar, indicating little differential impact between urinary and bowel function and bother on overall quality of life measured with the FACT.

Strengths of this study include the large sample size of women from 88 institutions in three countries and the inclusion of women receiving two different doses of radiation following hysterectomy, some of whom received chemotherapy. Although not a primary focus of this validation, similar results were obtained among women who did and did not receive chemotherapy (Tables S1 and S2). The majority of the women were white and non-Hispanic, limiting the generalizability of the results. Despite this limitation, however, the in depth validation presented in this paper extends the validation previously conducted in men, providing additional support for the use of this instrument in assessing the extent of, and impact from, radiation induced toxicity to the pelvis in all patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Conflict of Interest Statement

Dr(s). Bruner, Cantuaria, Chang, Doncals, Ferguson, Gaffney, Gil, Haas, Kachnic, Kim, Klopp, Kundapur, Mohan, Wenzel, Yaremko, Yeung, and Snehal Deshmukh have nothing to disclose. Dr. Pugh discloses funding from Millenium to her institution for a prostate cancer trial. Dr. Small discloses he is co-chair of the NRG BYN committee and receives a salary that is forwarded to his institution for this position. Dr. Thompson discloses employment with the University of Oklahoma. Dr. Westin reports grants, personal fees and non-financial support from AstraZeneca, personal fees from Takeda, personal fees from BioAscend, personal fees and non-financial support from Clovis Oncology, personal fees from ACI Clinical/Xenetic Biosciences, personal fees from Syndax/Watermark, personal fees and non-financial support from Genentech, grants from Bayer, grants from COTI, grants from Novartis, grants from Tesaro, outside the submitted work.

This project was supported by grants U10CA180868 (NRG Oncology Operations), U10CA180822 (NRG Oncology SDMC), UG1CA189867 (NCORP) from the National Cancer Institute (NCI).

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Highlights

- Cronbach's alpha for bowel and urinary domains at five weeks were very similar to those in the validity study with men.
- Correlations suggested the bowel and urinary domains are measuring conceptually discrete components of health.
- EPIC bowel and urinary domains provided valid assessment of toxicity in women undergoing postoperative radiation therapy.

Table 1.

Patient Characteristics

	IMRT (n=129)	Standard RT (n=149)	Chi-square p-value
Age (median age in years, range)	62 (28–82)	61 (29–83)	0.46 *
Race (n, %)			
American Indian or Alaskan Native	3 (2.3%)	1 (0.7%)	n/a
Asian	12 (9.3%)	17 (11.4%)	
Black or African American	13 (10.1%)	12 (8.1%)	
Native Hawaiian or Other Pacific Islander	0 (0.0%)	2 (1.3%)	
White	96 (74.4%)	114 (76.5%)	
Unknown	5 (3.9%)	3 (2.0%)	
Ethnicity (n, %)			
Hispanic or Latino	7 (5.4%)	15 (10.1%)	0.20
Not Hispanic or Latino	119 (92.2%)	133 (89.3%)	
Unknown	3 (2.3%)	1 (0.7%)	
Radiation dose (n, %)			
45 GY	76 (58.9%)	84 (56.4%)	0.67
50.4 GY	53 (41.1%)	65 (43.6%)	
Disease Site (n, %)			
Endometrium	108 (83.7%)	125 (83.9%)	0.97
Cervix	21 (16.3%)	24 (16.1%)	
Chemotherapy (n, %)			
No Chemotherapy	95 (73.6%)	112 (75.2%)	0.77
Cisplatin at 40 mg/m^2 weekly for 5 weeks	34 (26.4%)	37 (24.8%)	

* p-value from two-sided t-test

n/a: Chi-square not valid due to small expected cell count

Table 2.

Standardized Cronbach's Alpha for Bowel and Urinary Domain Summary and Subscale Scores at Baseline, 3 weeks, 5 weeks and 4 – 6 weeks post RT

	Baseline	3 Weeks	5 Weeks	4 – 6 Weeks Post RT
Bowel Summary	0.77	0.89	0.89	0.89
Bowel Function	0.48	0.72	0.71	0.70
Bowel Bother	0.78	0.86	0.88	0.89
Urinary Summary	0.84	0.87	0.89	0.89[1]
Urinary Function	0.63	0.73	0.73	0.74[1]
Urinary Bother	0.77	0.82	0.86	0.85[1]
Urinary Irritation	0.69	0.74	0.79	0.74[1]
Urinary Incontinence	0.91	0.91	0.92	0.91

[1]Raw Cronbach's alpha is provided since questions 'how often have you urinated blood?' and 'bleeding on urination' received the same response (rarely or never, and no problem, respectively) from all patients which did not allow the standardized Cronbach' s alpha to be calculated.

Table 3.

Correlations between Bowel and Urinary Domain Subscale Scores

	Bowel Function	Bowel Bother	Urinary Function
Baseline (n=276)			
Bowel Bother	0.63 *		
Urinary Function	0.23 *	0.33 *	
Urinary Bother	0.37 *	0.44 *	0.70 *
Week 3 of RT (n=245)			
Bowel Bother	0.81 *		
Urinary Function	0.23 *	0.22 *	
Urinary Bother	0.43 *	0.49 *	0.67 *
Week 5 of RT (n=241)			
Bowel Bother	0.81 *		
Urinary Function	0.25 *	0.32 *	
Urinary Bother	0.43 *	0.53 *	0.74 *
4 – 6 Weeks Post RT (n=227)			
Bowel Bother	0.79 *		
Urinary Function	0.44 *	0.52 *	
Urinary Bother	0.47 *	0.56 *	0.75 *

* $p<0.001$

Table 4.

Correlations between Bowel and Urinary Summary Scores and FACT-G at Baseline, 5 weeks, and 4 – 6 weeks post RT

	Baseline	5 Weeks	4 – 6 Weeks Post RT
Bowel Summary	0.44 *	0.44 *	0.44 *
Urinary Summary	0.39 *	0.43 *	0.40 *

Higher scores on both instruments indicate better QOL.

* p<0.0001

Table 5.

Correlations between Bowel and Urinary Summary Scores and FACT -TOI at Baseline, 5 weeks, and 4 – 6 weeks post RT

	Baseline	5 Weeks	4 – 6 Weeks Post RT
Bowel Summary	0.47*	0.53*	0.51*
Urinary Summary	0.47*	0.54*	0.53*

Higher score s on both instruments indicate better QOL.

*p<0.001

Table 6.

Correlations between Bowel and Urinary Summary Scores and PRO-CTCAE Items at Baseline, 5 weeks, and 4 – 6 weeks post RT

	Baseline		5 Weeks		4 – 6 Weeks Post RT	
	Bowel Summary	**Urinary Summary**	**Bowel Summary**	**Urinary Summary**	**Bowel Summary**	**Urinary Summary**
Pain in Abdomen						
Severity	−0.54 *	−0.27 *	−0.62 *	−0.44 *	−0.52 *	−0.37 *
Interference	−0.48 *	−0.20 **	−0.62 *	−0.42 *	−0.47 *	−0.29 **
Loose or Watery Stools						
Frequency	−0.37 *	−0.14	−0.79 *	−0.31 *	−0.63 *	−0.26 **
Loss of Bowel Movement Control						
Frequency	−0.28 *	−0.19 **	−0.49 *	−0.26 *	−0.60 *	−0.42 *

Higher scores on the PRO-CTCAE indicate increased frequency/severity/interference; higher scores on the bowel and urinary domains scores indicate better QOL.

* p<.001

** p<.01