Cross validation of the prostate cancer radiotherapy late toxicity (PCRT) questionnaire with the expanded prostate cancer index composite (EPIC) instrument

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Introduction: *A 29-item prostate cancer radiotherapy (PCRT) questionnaire with genitourinary (GU), gastrointestinal (GI), and sexual (S) domains has been previously validated for the assessment of late toxicity health-related quality of life (HRQoL) effects. The study objective was to cross-validate the PCRT domains versus the expanded prostate cancer index composite (EPIC) questionnaire urinary (U), bowel (B), hormonal (H), and S subscales.*

Methods and materials: *A single-institution cross-sectional PCRT patient cohort was surveyed. Descriptive and intra- and inter-class correlation coefficient statistics for the various EPIC and PCRT HRQoL domain scores were generated. Univariable and multivariable Cox and logistic regressions were performed depending on the HRQoL endpoint being assessed.*

Results: *A total of 189/276 patients (68%) completed questionnaires with EPIC and PCRT missing data rates of 9% and 4%, respectively. Mean age was 75.8 years (SD 5.5) and the mean time of questionnaire completion after radiotherapy was 852 days (range 212-1454 days). Mean EPIC urinary (85.1 SD 12.9), bowel (84.1 SD 15.8), sexual (21.8 SD 20.7), and hormonal (85.3 SD 13.7) as well as PCRT genitourinary (66.1 SD 15.3), gastrointestinal (83.6 SD 14.3), and sexual (39.4 SD 21.6) domain scores were calculated. Intraclass correlation coefficients comparing corresponding EPIC/PCRT domains ranged from 0.50-0.88. Interclass correlation coefficients for non-corresponding EPIC/PCRT domains ranged from 0.16-0.43 and 0.23-0.30, respectively. EPIC B/U, PCRT GI/GU and PCRT S required arcsin square root transformation and EPIC S/H domains required dichotomous transformations prior to univariable/multivariable analyses. Multivariable analysis demonstrated novel associations between predictive variables and HRQoL domains including between the PTV-bladder overlap volume and PCRT GU score.*

Conclusions: *The PCRT is a compact, valid, and HRQoL instrument with very high questionnaire compliance rates and similar statistical properties to the EPIC instrument. However, dichotomization of the PRCT S data was not required which suggests some potential statistical advantage to the PCRT.*

Key Words: prostate cancer, health-related quality-of-life, cross-validation, late toxicity, radiotherapy

Introduction

Strategies (alone or in combinations) for the treatment of non-metastatic prostate cancer routinely include: external beam radiation therapy (EBRT), radical prostatectomy (RP), permanent low dose rate (LDR) brachytherapy (LD), temporary high dose rate brachytherapy, and various forms of hormonal manipulation.[1] Establishing the relationship between tumor control and treatment related toxicities; otherwise known as the therapeutic ratio, is necessary for rational physician and patient treatment decision-making in prostate cancer. Specifically in terms of prostate cancer; control is usually described in terms of outcome concepts such as biochemical failure free survival, metastasis-free

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survival, prostate cancer specific survival and overall survival. Treatment related toxicities are usually captured with the use of toxicity scales and/or health-related quality of life instruments.[2]

Toxicity scales have been developed and utilized to grade relevant prostate cancer treatment side effects including those affecting the sexual, bowel, bladder, and hormonal domains. These scales have included those from the RTOG, EORTC, LENT-SOMA, and NCI-CTC systems.[2] Although the aforementioned scales are not generally complicated to use, they are constrained in the type and intricacies of the information that can be captured. Specifically, these scales are not able to measure the impact on health-related quality-of-life (HRQoL) related to treatment side effects. For instance, most of these scales do not measure the level of bother that the symptom causes to the patient; they primarily capture the presence and severity of symptoms.

Given the introduction of newer radiation modalities of treatment such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy, high dose rate brachytherapy, and proton therapy; the measurement of patient-reported late toxicities specific to radiotherapy are becoming increasing important. Several prostate cancer HRQoL questionnaires have been reported in the literature to assess the patient reported impact of therapy.[3-13] An example, of a generic instrument designed commonly used to assess prostate-specific cancer HRQoL in a variety of treatment scenarios is the expanded prostate cancer index composite (EPIC).[7] Recently, the prostate cancer radiation toxicity (PCRT) questionnaire was developed to specifically assess both the severity and bother of patients symptoms related to the late effects of prostate radiotherapy using a HRQoL construct.[10] This instrument was created to fill a need for a patient reported questionnaire focusing on late toxicities related to prostate radiotherapy in order to provide clinicians relative toxicity information across various radiotherapy modalities and approaches either in the context of clinical trials or clinical practice. The PCRT instrument has recently successfully completed initial cross-validation procedures versus other HRQoL questionnaires such as the SF-36 (general health HRQoL questionnaire), the FACT-G (general cancer HRQoL questionnaire) and the PCQoL (a prostate cancer specific HRQoL questionnaire). The primary goal was the further validation of the PCRT questionnaire versus the commonly used EPIC questionnaire. The secondary goal of this investigation was to perform univariable and multivariable prediction analyses of pretreatment factors with the EPIC/PCRT HRQoL domains.

Methods and materials

Study design

The study design is an observational cross-sectional postal survey with retrospective chart based baseline data collection, and was primarily employed to perform a cross-validation comparison of the PCRT questionnaire with the EPIC questionnaire. This research project was approved by the University of Western Ontario Institutional Review Board prior to study initiation. All patients provided informed consent by means of a letter of information and consent form as part of the study package mailed out to all possible participants. The postal package included a copy of the EPIC questionnaire followed by a PCRT questionnaire as well a cover sheet with instructions regarding informed consent, questionnaire content, and instructions for returning the questionnaires by means of a stamped return envelope to the study investigators. One follow up phone call at 4 weeks post mailing was performed to individuals who did not return the questionnaire in order to ensure that the individual had received the package and to answer any questions regarding the study.

The primary study population is comprised of a cohort of pathologically confirmed prostate cancer patients treated with external-beam radiotherapy with a dose of 73 Gy in 35 fractions between the years 2003 and 2007. Patients needed to be able to fill out questionnaires in English and were required to have at least 6 months follow up post-radiotherapy prior to entry into this study (questionnaire mailing occurred July 2008). Once all questionnaire were returned from participating subjects, a retrospective review of various clinical (age, medical comorbidities, baseline GI/GU functioning, use of anticoagulation, previous cancer(s)), tumor (history of TURP, PSA, Gleason grade, T and N stage), and treatment (radiotherapy clinical volumes, PTV overlap with rectum and bladder, prostate volume) factors was conducted for later descriptive and univariable/multivariable analyses. All study data entry was completed as of December 2008.

Study questionnaires

Two validated HRQoL measurement questionnaires were used for our study: the 32 item EPIC questionnaire (generic prostate-HRQoL instrument providing a summary of HRQoL), is a validated instrument assessing five HRQoL domains including urinary (U), bowel (B), sexual (S), hormonal (H) and patient satisfaction and ten related subscales.[7] Each EPIC domain can be reported as either a total score or separated into separate function (F) and bother (B) subscores. The second questionnaire utilized was the 29 item PCRT questionnaire, which

is also a validated instrument specifically measuring the HRQoL late toxicity impacts of prostate cancer radiotherapy.[10] The PCRT questionnaire reports on three domains: GU, GI, and sexual(S). The PCRT GU urinary domain included five late toxicity symptoms including nocturia, frequency, dysuria, hematuria, and incontinence. The PCRT GI bowel domain included four symptoms including diarrhea, pelvic pain, tenesmus, and bowel control. The PCRT sexual domain included three symptoms including impotency, libido, and contentment. In addition, imbedded with the PCRT instrument is the ability to abstract patient-reported RTOG late GI and GU toxicity scales. Thus the PCRT can be utilized, in the context of a clinical trial or clinical database systems, to acquire patient reported late toxicity grades that can then be confirmed/adjusted by medical staff prior to data entry. All multi-item scale scores for the PCRT/EPIC have been transformed linearly to a 0-100 scale, with higher scores representing better HRQoL. Permission to use these questionnaires was obtained from the corresponding authors listed in the validation manuscripts.

Sample size calculation

A sample size calculation for this investigation was performed using the SISA online calculator (http://www.quantitativeskills.com/sisa/calculations/samsize.htm). We assumed that the smallest clinically significant cross correlation between the PCRT and EPIC domains would be those with a Pearson product-moment correlation coefficient of 0.2 or greater (therefore, r = 0.20 alternative hypothesis population correlation versus r = 0.0 null hypothesis population correlation). In this way a two-sided t-test sample size of 194 subjects with alpha = 0.05 and 80% power assumptions was calculated. Considering a potential combined 50% enrollment refusal, loss to follow up, and missing data rate, the final adjusted sample required to approach with regards to this study would be equal to 291 subjects. An Ontario patient information system (OPIS, Cancer Care Ontario) query was performed prior to initiation of the protocol which confirmed that 299 patients with appropriate inclusion criteria were potentially available to be approached with regards to this project. Having subsequently identified four deceased patients and 19 other patients that were lost to follow up, we mailed out questionnaires to 276 patients.

Statistical analysis

Descriptive statistics were generated in order to describe the study population demographics, baseline characteristics and PCRT/EPIC domain scores. Additional analyses assessed the correlation between and within the EPIC and PCRT questionnaires. Internal consistency reliability was assessed by employing intraclass correlation analysis, construct/concurrent validity by calculating the Pearson correlation coefficient (interclass correlation) between PCRT and EPIC subscales. We also assessed the convergent/discriminant validity of the PCRT instrument by calculating the Pearson correlation coefficient between all subscales of the PCRT. A Pearson correlation coefficient of 0.5 and higher was considered to demonstrate evidence of strong linear association. Additionally, coefficient values of 0.2 to 0.49 were considered to be moderate in nature and values less than 0.20 were considered to exhibit either little or no significant correlation between measures.

We performed univariable and multivariable analyses of baseline factors in the prediction of post-treatment PCRT/EPIC domain scores. To ensure that data fitted the proposed multiple regression model, an initial univariable analyses was performed. Histograms with box plots were used to report the non-normal errors of distribution. Furthermore, the univariable statistical analysis procedure was used to test for outliers and normality of the domain distribution in question (Skewness, Kurtosis and Shapiro-Wilk W statistics). For non-normal and/or highly skewed data, data transformation by either arcsin square root (ASSR) transformation or dichotomization of domain data was used as necessary in order to satisfy regression analysis assumptions. Variables that met the statistical significant associations (p value < 0.1) in the univariable analysis, were entered into the stepwise multivariable logistic regression analysis. Multiple linear regressions were used for continuous outcomes and logistic regression for the transformed sexual domain for both EPIC/PCRT. All analyses were performed with the SAS system (SAS Inc., Cary, NC, USA).

Results

Study population

A total of 189 completed questionnaires out of 276 mailed questionnaires were returned; thus, a study response rate of 68% was achieved. The mean interval time between end of RT and questionnaire completion was 851.6 days (range 212-1454 days). Detailed descriptive continuous and tabular statistics for the study patients are listed in Tables 1 and 2, respectively. The mean age of the study population was 76 years (range 53 to 84 years). The mean TRUS volume (available on n = 167) was 51 cc with range (18 cc-238 cc). Of the 189 patients in the study population, 25 had a TURP procedure at some point in the past (13%).

TABLE 1. **Pretreatment patient demographics and characteristics**

Variable	Mean	Std Dev	Min	Median	Max
Age	75.77	5.54	53.00	77.00	84.00
TRUS volume (cm^3)	51.15	31.52	18.00	42.00	238.0
PSA pre-treatment (ng/mL)	12.48	12.07	0.01	8.79	77.50
PSA nadir (ng/mL)	0.70	1.18	0	0.18	11.50
PSA at failure (ng/mL)	6.59	3.19	2.030	6.50	10.90
PSA prior to questionnaire (ng/mL)	0.59	0.95	0	0.20	7.38
Most recent PSA (ng/mL)	0.54	1.07	0	0.24	10.90
Interval between end of RT & questionnaire administration (days)	851.6	335.0	212.0	896.00	1454
PTV volume (cm^3)	153.13	44.56	57.46	146.65	312.0
Rectal volume (cm^3)	69.74	47.17	27.86	61.86	482.7
Bladder volume (cm^3)	161.86	82.67	45.70	144.99	467.7
PTV rectal overlap volume (cm^3)	8.55	3.21	2.81	7.98	25.05
PTV bladder overlap volume (cm^3)	18.27	7.30	6.96	17.84	35.75

TRUS = transrectal ultrasound; PSA = prostate specific antigen
RT = radiotherapy; PTV = planning target volume

Mean pretreatment PSA was 12.5 ng/mL. Gleason score distribution was 2-6 in 36%, 7 in 41%, and 8-10 in 23% of patients.

TABLE 2. **Study cohort treatment and risk stratification variables (n = 189)**

Variable	Frequency	Percent
Treatment volume		
Prostate only	27	14.3
Prostate and seminal vesicles	112	59.3
Prostate and seminal vesicles and pelvic	50	26.5
Biopsy Gleason score distribution		
2-6	68	36.2
7	77	41.0
8-10	43	22.8
Clinical T-stage		
T1	64	33.9
T2	101	53.4
T3	22	11.6
TX	2	1.1
N-stage		
N0	135	71.4
N1	7	3.7
NX	47	24.9

T = tumor; N = node

All patients were planned using three-dimensional conformal simulation and planning techniques using a class solution based simultaneous in-field boost technique to total doses of 44 Gy (pelvic lymph nodes), seminal vesicles (54 Gy) and prostate (73 Gy) in a total of 35 fractions. Uniform 1 cm PTV margins were used and customized planning and/or image guidance (using daily ultrasound imaging, Re-Situ, Resonant Medical, Montreal, Canada) for those patients where calculated overlap of the PTV with rectum or bladder exceeded institutional thresholds. Choice of treatment volume was at the attending radiation oncologist's discretion. One-hundred and twelve (59%) study patients received treatment to both the prostate and seminal vesicles with a smaller proportion of patients (50/189, 26%) receiving whole pelvic radiotherapy. Ninety-nine (52%) of participants had received hormonal therapy (LHRH agonist ± antiandrogens) at some point in their disease course. Of those receiving hormone therapy, 96% of patients received neoadjuvant hormone therapy, 68% received adjuvant hormone therapy, and 61% received concurrent hormone therapy with radiotherapy; 33/189 (17.4%) of the entire study cohort were receiving hormonal therapy at the time of the questionnaire. Only one patient had experienced biochemical failure at the time the questionnaire was administered.

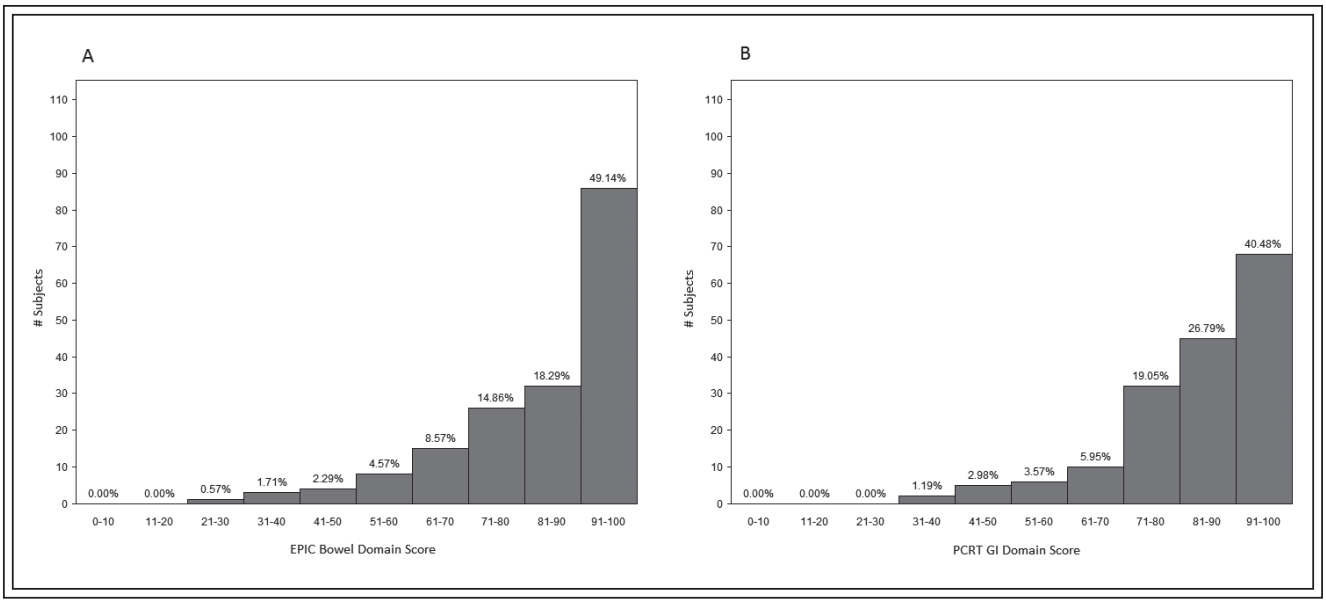

Figure 1. Histogram of EPIC/PCRT bowel/gastrointestinal scores.

PCRT and EPIC descriptive analyses

Of the 189 questionnaires returned to the study investigators, missing items in the EPIC and PCRT questionnaires, was 9% and 4% respectively. The EPIC U, B, S, hormonal, and patient satisfaction domain scores (mean ± SD) were 85 ± 13, 84 ± 16, 23 ± 21, 85 ± 14, and 82 ±2 4 respectively (higher score corresponding to higher quality-of-life). The highest urinary subdomain score was 92 ± 12 for urinary function, and the lowest was 81 ± 18 for urinary bother with urinary incontinence and urinary irritative scores. The B function subdomain score was 86 ± 14 and B bother subdomain score was 82 ± 20. Sexual subdomain scores of 14 ± 19 and 41 ± 38 for sexual function and sexual bother were observed, respectively. The PCRT domains GU, GI, and S (mean ± SD) were 66 ± 15, 84 ± 14, and 39 ± 22, respectively. Probability distribution histograms comparing corresponding PCRT-EPIC GI/B, GU/U, and S domain scores are illustrated in Figures 1, 2, and 3, respectively.

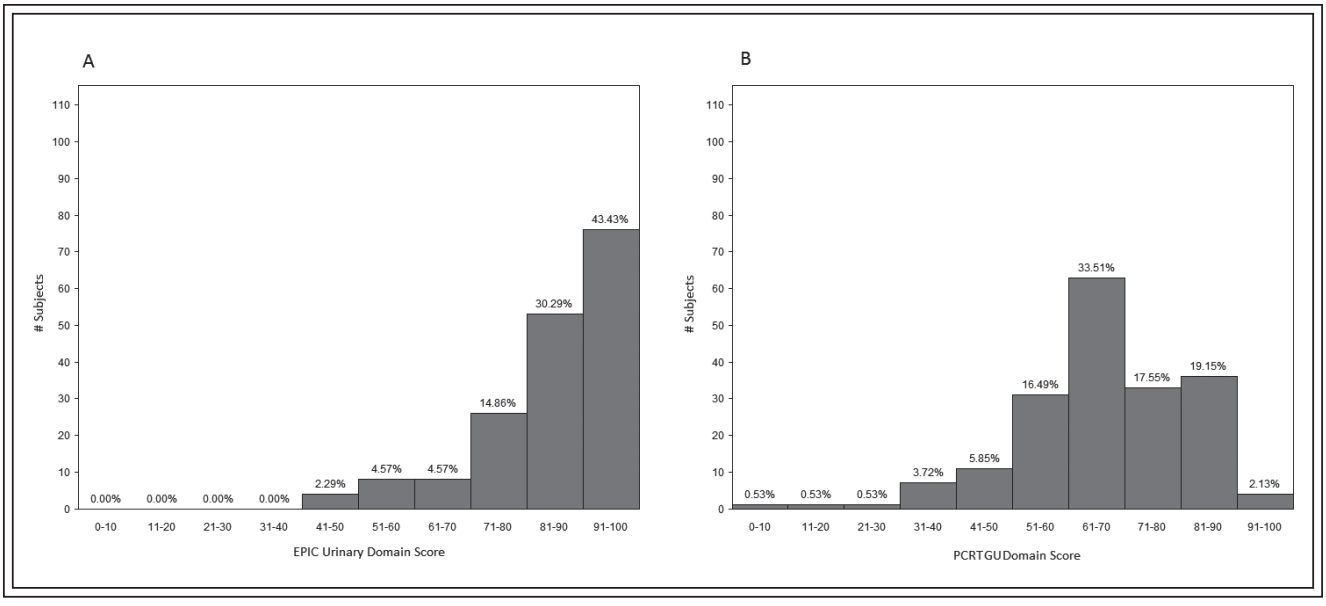

Figure 2. Histogram of EPIC/PCRT urinary/genitourinary scores.

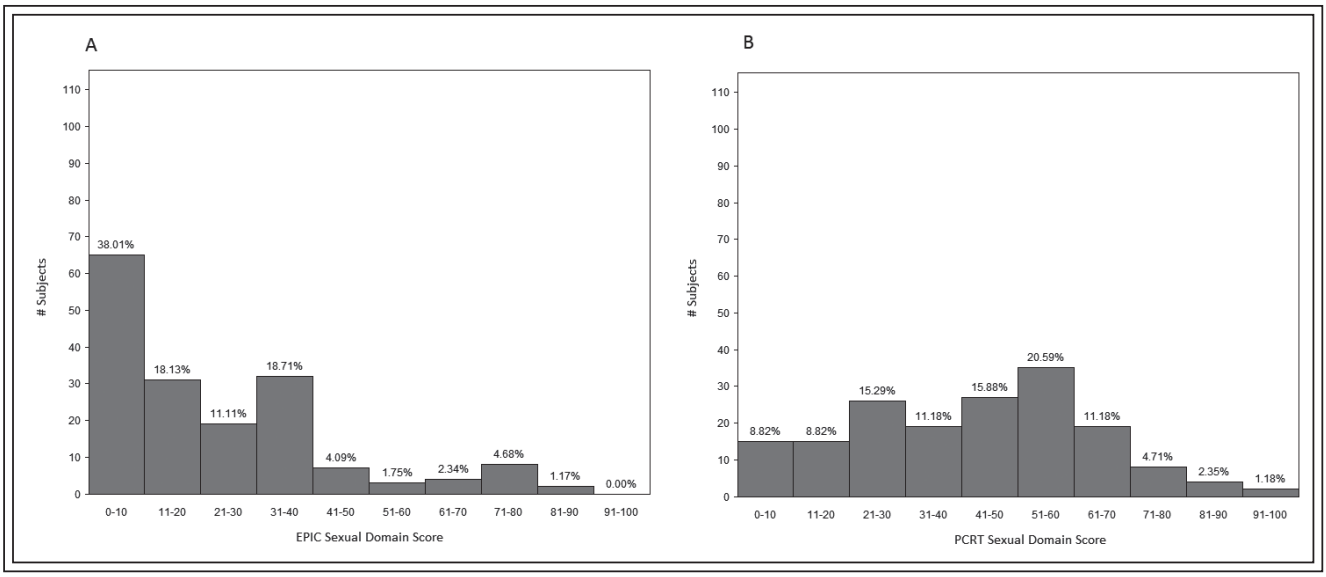

Figure 3. Histogram of EPIC/PCRT sexual scores.

PCRT and EPIC internal consistency

Internal consistency intraclass correlation coefficients were 0.30, 0.29, and 0.23 (all $p < 0.05$ for all comparisons to zero correlation) for PCRT GU-GI, GU-sexual, and GI-sexual cross domain comparisons, respectively. These internal correlations between PCRT domains demonstrate associations between concepts measuring related but not overlapping HRQoL concepts. Similarly, intraclass correlation coefficients examining the relationship between the different EPIC domains ranged from 0.16 (sexual-B comparison, $p = 0.03$) to 0.43 (U-B comparison, $p < 0.0001$). These internal consistency results mirror those from previously published validation studies for both the PCRT and EPIC questionnaires.[7,10]

PCRT – EPIC cross validation

The cross validation analysis was conducted by calculating the interclass correlation coefficients between the two questionnaires (EPIC and PCRT). All p values represent a statistical comparison of an alternative hypothesis of a non-zero correlation coefficient to the null hypothesis of zero correlation between the relevant domains/subscales. Table 3 presents the correlation coefficient analysis between the three PCRT domains and the 5 EPIC domain and 10 subscales. Therefore, these correlation matrixes indicate significant evidence of a strong and moderate linear association between PCRT GI, GU, sexual domains and the respective EPIC domains and subscores.

The PCRT GI and EPIC B domains demonstrated the strongest positive linear association with an r value of 0.88 which demonstrates a near perfect correlation. Similarly, correlation between the PCRT GI and the EPIC B subscales of bother and function ranged from 0.74 to 0.88 have significant strong association with almost perfect correlation of 0.9. The above strong correlations of the GI organ system indicate that both questionnaire scales tend to converge but are not identical. Conversely, the scales belonging to different organ systems tend to diverge as may be expected in the assessment of correlation between two related but distinct HRQoL concepts (i.e. the correlation between PCRT GI and other EPIC non-B scales ranged from 0.13 to 0.32). Similar correlation patterns were seen in the GU/U and sexual domains (and EPIC subscales). Correlation coefficients between corresponding domains ranged from 0.52 to 0.72 and 0.49 to 0.66 for GU/U and S domain/subscale comparisons, respectively. In general, these corresponding domain/subscale correlations would be considered to be moderate, particularly compared to the GI/B correlations observed in the context of the cross validation study. Correlation coefficients for non-corresponding domains/subscales ranged from 0.17 to 0.40 and 0.12 to 0.31 for GU/U and S domain/subscale comparisons, respectively.

Univariable and multivariable analyses

EPIC B/U/H and PCRT GI/GU domains demonstrated significant negative skewness (distribution concentrated to the higher HRQoL values) with a significant positive skew to lower HRQoL scores for the EPIC S domain. Only the PCRT S domain did not have any significant

TABLE 3. **Interclass correlation coefficients between EPIC and PCRT HRQoL scores**

	PCRT domains		
EPIC domains	**GI-PCRT r (n/p)**	**GU-PCRT r (n/p)**	**Sexual-PCRT r (n/p)**
Urinary	0.297 (155, p = 0.002)	**0.717 (176, p < .0001)**	0.311 (159, p < .0001)
Urinary function	0.178 (169, p = 0.02)	**0.523 (189, p < .0001)**	0.258 (171, p = 0.007)
Urinary bother	0.321 (154, p < .0001)	**0.727 (175, p < .0001)**	0.291 (158 p = 0.0002)
Urinary irritative	0.296 (154, p = 0.0002)	**0.647 (175, p < .0001)**	0.238 (158, p = 0.0026)
Urinary incontinence	0.184 (154, p = 0.0221)	**0.593 (175, p < .0001)**	0.260 (158, p = 0.001)
Bowel	**0.877 (155, p < .0001)**	0.401 (175, p < .0001)	0.242 (158, p = 0.0022)
Bowel function	**0.742 (165, p < .0001)**	0.353 (185, p < .0001)	0.179 (167, p = 0.0210)
Bowel bother	**0.882 (154, p < .0001)**	0.373 (174, p < .0001)	0.250 (157, p = 0.0016)
Sexual	0.179 (153, p = 0.02)	0.266 (170, p = 0.0004)	**0.667 (159, p < .0001)**
Sexual function	0.135 (150, p = 0.099)	0.231 (169, p = 0.0025)	**0.497 (160, p < .0001)**
Sexual bother	0.164 (146, p = 0.048)	0.216 (161, p = 0.006)	**0.623 (151, p < .0001)**
Hormonal	0.289 (154, p = 0.0003)	0.353 (174, p < .0001)	0.228 (158, p = 0.004)
Hormonal function	0.211 (164, p = 0.007)	0.335 (184, p < .0001)	0.185 (168, p = 0.016)
Hormonal bother	0.313 (156, p < .0001)	0.325 (176, p < .0001)	0.269 (159, p = 0.0006)
Satisfaction	0.259 (167, p = 0.0007)	0.173 (187, p = 0.018)	0.120 (169, p = 0.1193)

GI = gastrointestinal; GU = genitourinary; r = correlation coefficient; n = number of patients; p = p value for comparison to zero correlation. Comparison between corresponding PCRT and EPIC domains/subscores presented in bold.

skew (skewness parameter 0.09) to the distribution. All EPIC and PCRT domains except for PRCT S had significant kurtosis (parameters ranging from 0.74-1.36 reflecting the thick tails in the distribution). The PCRT S domain had a small level of negative kurtosis (parameter -0.37 reflecting a thin tail in the distribution). All EPIC and PCRT domains were found to have non-normal distributions based on the Shapiro-Wilk statistic ranging from 0.88-0.98 (EPIC, all $p < 0.0001$) and 0.90-0.98 (PCRT, all $p < 0.01$). Based on this analysis, the EPIC GI/GU and all PCRT domains were subjected to an ASSR transformation in order to improve the normality of the distribution prior to univariable and multivariable analyses. EPIC S and H domains required dichotomization of the data (S domain score ≤ 15 versus > 15 and H domain score ≤ 90 versus > 90) as the ASSR transformation failed to normalize the data prior to statistical analyses within the context of this population.

Univariable analyses were performed on all domain endpoints in order to identify potential predictive variables for inclusion into multivariable modelling. No variables were found to associate with EPIC S, H, and PCRT S. The following relationships were determined on multivariable modelling of the remaining HRQoL domain endpoints: EPIC U (baseline GU assessment and use of blood thinners at baseline), EPIC B (use of concurrent hormonal therapy), PCRT GU (baseline GU assessment and PTV-bladder overlap volume), and PCRT GI (use of TURP prior to radiotherapy).

Discussion

A variety of HRQoL questionnaires related to prostate cancer exist in the literature[3-13] which have been reviewed recently.[2,13] This selection of questionnaires allows for choice with regards to the optional utilization of either stand alone questionnaires[6-12] or those that are modules to generic[3,5,13] HRQoL instruments. The PCRT was originally developed by a process of item generation from a literature search followed by questionnaire construction following multiple discussions with practitioners, experts and patients.[10] Initial pilot testing on 37 patients was performed in order to obtain patient feedback which did lead to some minor changes in the questionnaire format and content. An item reduction phase involving one-hundred patients demonstrated that several questions related to dysuria and hematuria should be removed due to the extremely low heterogeneity of response or frequency of occurrence. Reliability testing on 237 patients of the final GU, GI, and S item-

reduced subscales demonstrated favorable intraclass correlation coefficients (CC) of 0.811 (GU), 0.842 (GI), and 0.740 (sexual). Discriminant validity testing on 274 patients demonstrated Pearson CC of 0.449 (GU-GI), 0.200 (sexual-GU), and 0.09 (sexual-GI). Content validity versus other questionnaires including the prostate cancer quality of life (PCQoL), the functional assessment of cancer therapy - general (FACT-G), and the short form-36 (SF-36) was performed.[11,14-15] The correlations between PCRT-PCQoL were 0.35-0.78, PCRT-FACT-G were 0.19-0.39 and PCRTSF-36 were 0.03-0.34 which did demonstrate the content validity of the PCRT questionnaire.

The PCRT questionnaire has also been utilized in the assessment of late treatment-related toxicity and symptom bother associated with post-prostatectomy radiotherapy in 171 patients.[16] In this prospective cross-sectional cohort study, the PCRT instrument was able to characterize the patient population in terms of ongoing symptom dysfunction and bother with a typical PCRT survey response rate of 65%. PCRT impairment subscales were reported as mild for GI, moderate for GU and marked for S with mean PCRT domain scores of 91.8, 60.0, and 33.7, respectively. Specifically, the use of incontinence pads daily was reported by 25.6% and was similar to 23% use reported at baseline. Frequent or worse urinary frequency or hematuria was reported by 4.8%. Moderate to severe disruption from bowel and bladder dysfunction was reported by up to 5.4% and 2.4% of respondents, with a non-satisfaction rate of 42.7%.

The current investigation of the PCRT questionnaire in cross-comparison with the EPIC questionnaire assessed a patient population with higher age, Gleason score, and radiotherapy dose (73 Gy versus 70 Gy) and pelvic field utilization when compared to the initial PCRT validation study.[10] Mean PCRT GU, GI, and S domain scores as well as the discriminant validity comparisons were consistent between this investigation and the initial validation paper. This investigation has demonstrated that the PCRT instrument measures gastrointestinal, genitourinary, and sexual domains in a similar fashion to EPIC. Also, we identified various pretreatment predictive variables such as baseline GU functioning, use of blood thinners, PTV-bladder overlap volume, and history of TURP that were found to potentially predict for various HRQoL scores. These associations will need to be confirmed by other correlative studies prior to acceptance of a true relationship. The PCRT has the advantage of brevity and being a questionnaire specifically targeted towards the evaluation of late dose-limiting toxicities of prostate radiotherapy. Additionally, within the context of our dataset, the PCRT S domain had the statistical advantage of minimal skewness allowing for more efficient analysis of this domain. The EPIC questionnaire still has the advantages of a longer track record, subdomains measuring bother and function, as well as comparative data between different treatment approaches. Additionally, a shorter version of the EPIC has been recently psychometrically evaluated.[17] The PCRT is not designed for cross-therapy comparison; it is more specifically designed for the evaluation of various prostate cancer radiotherapy interventions/techniques that may directly positively (or negatively) impact of toxicity rates and severity.

The limitations of the study (and of the PCRT questionnaire) include the following: the PCRT is validated in external-beam RT and brachytherapy populations only (surgery, chemotherapy populations not studied), the PCRT is designed to assess late (> 6 months) effects of treatment, the PRCT subscales have not been cross-validated against existing late toxicity scales, or other toxicity risk factors such as DVH parameters. The responsiveness of PCRT subscales over time has not been determined; however, the assessment of the responsiveness of the PCRT questionnaire is a secondary outcome of an ongoing multi-institutional randomized clinical trial assessing 3DCRT versus helical tomotherapy (image guided intensity modulated radiotherapy) for high risk prostate cancer (clinicaltrials.gov registry - NCT00326638). An acute version of the questionnaire has been developed and will be tested in conjunction with a prospective clinical trial to assess its' full psychometric properties including reliability, validity, and responsiveness.

Future development of the PCRT questionnaire can include an assessment of other populations that receive external-beam RT for prostate cancer which would generate additional information regarding the PCRT questionnaire. Study of subpopulations of RT patients (nodal RT versus prostate alone, moderately high versus high dose RT, altered radiotherapy schedules) may also be performed.

Integration of the PCRT questionnaire into clinical trials assessing novel radiation techniques, dose escalation and dose per fraction escalation can be performed. The assessment of various newer treatment delivery paradigms/systems such as proton therapy, SBRT, volumetric arc therapy as well as the impact of image-guided radiation therapy procedures require validated toxicity and HRQoL instruments, such as the PCRT, to assess potential improvements in technique within the prostate cancer setting. Potential randomized phase II or III studies could use the PCRT

as either a primary (phase I/II safety assessment) or secondary (phase III superiority or equivalence trial) endpoint. Correlation with existing late toxicity scales and dosimetric/DVH parameters could potentially be another avenue for investigation. Routine intermittent administration of this questionnaire in the setting of post-radiation therapy follow up could serve as a screening questionnaire to detect negative quality-of-life effects due to the late toxicities of prostate radiation therapy. Identified individuals with large changes in late toxicity quality of life scores can be subsequently subjected to appropriate diagnostic, therapeutic, and educational programs to mitigate these negative quality-of-life effects.

Conclusions

The PCRT is a compact, valid, and HRQoL instrument with very high questionnaire compliance rates and similar statistical properties to the EPIC instrument. This research has confirmed the PCRT as a psychometrically reliable and valid short questionnaire specifically assessing the HRQoL related to the late effects of prostate radiation therapy. Specifically to our dataset, dichotomization of the PRCT S data was not required which suggests some potential statistical advantage to the PCRT. In addition, the current iteration of the PCRT questionnaire allows for the abstraction of relevant RTOG GI and GU late toxicity endpoints thereby simplifying the need for multiple questionnaires/scores to collect toxicity and health-related quality-of life information. The PCRT HRQoL instrument may have important future applications in the long term clinical follow up/triage of radiation late effects. In addition, various clinical trial/research opportunities exist in association with such a targeted questionnaire. □

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