REVIEW

Toxicity and health-related quality-of-life assessment in prostate radiotherapy

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The use of radiation therapy in the radical treatment of prostate cancer can lead to potential acute and long-term toxicity and health-related quality-of-life (HRQoL) changes. Ongoing investigation into dose-escalation, dose-per-fraction escalation, new radiation treatment technology/paradigms, and novel systemic therapy may have either positive and/or negative effects on normal tissue toxicity/HRQoL. Herein, common toxicity scales and HRQoL instruments that attempt to describe the deleterious effects of prostate radiation therapy are reviewed.

Key Words: prostatic neoplasms, acute and late toxicity, health-related quality-of-life, questionnaires

Introduction

Both the morbidity and mortality of adenocarcinoma of the prostate continues to have a large impact on the Canadian population and health care resources. It is the most frequently diagnosed malignant neoplasm excluding skin malignancies and the third highest cause of cancer-related death in the Canadian male population.[1] Treatment of non-metastatic disease can depend on various factors including baseline PSA, T stage, Gleason score, prostate volume, patient age, comorbidities, and patient preference. Patients with low-risk prostate cancer have excellent survival with single modality radical treatment with radical prostatectomy (RP), external-beam radiation therapy (RT) or permanent trans-perineal brachytherapy seed implant. Patients with intermediate-risk prostate cancer may have increased risk of local, regional, and systemic relapse when treated with single modality therapy alone. The use of hormonal therapy and dose-escalated radiotherapy is being explored for these patients. An underlying hypothesis in radiation dose-escalation studies is that improved local control for primary tumors with higher doses of radiation will improve patient outcomes. Generally, the dose per fraction utilized in the radiation treatment of prostate cancer ranges from 1.8 Gy/day to 2.0 Gy/day. Preliminary level I evidence now exists that dose-escalation to 78 Gy using conventional dose per fraction (1.8 Gy/fraction - 2.0 Gy/fraction), particularly in intermediate- and high- risk patients, has improved PSA recurrence-free survival compared to standard treatment with 70 Gy.[2] For high-risk patients, randomized trial evidence supports the use of long-term adjuvant hormonal ablation in conjunction with standard dose RT resulting in clinically and

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statistically significant improvements in survival.[3] Other treatment modalities such as high-dose rate (HDR) brachytherapy, cryotherapy, high intensity focused ultrasound (HIFU) are undergoing various evaluations to determine the proper indication(s) for these modalities.

Bladder symptoms after treatment can be due to suboptimal baseline functioning, disease progression, new bladder pathology, or as a result of local radiation treatment effects. These late effects can include urinary frequency, nocturia, dysuria, hematuria and urinary incontinence. Radiation-induced bladder late effects are related to the total radiation dose and the bladder dose-volume relationship as well as baseline functioning. Rectal late toxicity effects may include diarrhea, tenesmus, and rectal bleeding. Rectal effects are associated with the total radiation dose, dose per fraction, treatment technique, rectal dose-volume relationships and underlying comorbid illness such as diverticulitis, diabetes mellitus and hypertension. Treatment with RT may also result in loss or diminished sexual function. Changes in sexual function may relate directly to the dose to the penile bulb and the neurovascular bundles.[6] However age, pre-treatment sexual functioning and other prostate cancer interventions (surgery and hormonal therapy) can have confounding effects as well. Standardized reporting of all these toxicities can facilitate high quality reporting from clinical trials and clinical practice.

The concept of therapeutic ratio is the relationship between tumor control and significant toxicities of treatment. The acute and long-term treatment-related morbidities associated with the various prostate cancer treatment options, such as RP, external-beam radiation, permanent brachytherapy seed implant, temporary HDR brachytherapy implant, and hormonal manipulation, can be significant.[4] Therefore, the concept of therapeutic ratio is important in defining the trade-off that patients accept for cure/control versus harm. Strategies incorporating radiation dose escalation (total dose and dose per fraction escalation) for augmenting local control rates require improvements in patient immobilization, prostate imaging and targeting, treatment delivery and verification. This increased level of technical sophistication is necessary in order to optimize the therapeutic ratio by adequately treating the tumor volume(s) of interest while respecting the tolerance of normal tissues such as rectum, bladder, penile bulb and the bilateral femoral heads.[5] Dose and dose-per-fraction escalation strategies to improve the prognosis of localized and locally advanced prostate cancer require a greater emphasis on the assessment and treatment of radiation-induced late effects. Validated methods of documenting late rectal, bladder, and sexual toxicity are required to complement tumor control data such as the biochemical-free, disease-free, and overall survival endpoints to ensure the therapeutic ratio is being optimized through these treatment innovations.

Late rectal, bladder and sexual effects have been historically graded using various ordinal toxicity scales and systems. These scales are usually easy to administer; however, they are limited in the type and complexity of the information captured. In addition, impact on health-related quality-of-life (HRQoL) of these side effects is not usually measured by these scales (i.e. these scales do not measure the impact or bother to the patient of a specific symptom). Potentially, patients may have high symptom grade and low impact/bother or conversely can have low symptom grade and high impact/bother. The other limitation of these scales is in the stepwise ordinal nature of the scales themselves. Small clinical changes are not usually detected by the traditional four-point toxicity scale. HRQoL instruments have been designed, in part, to attempt to detect small clinical changes in domains that matter to patients on a continuous scale. Various non-symptom specific HRQoL questionnaires have been constructed to assess HRQoL of patients with prostate cancer before, during and/or after various prostate cancer treatments (surgery, radiation, hormones, and brachytherapy). An understanding of these various scales and HRQoL instruments assist in the design and interpretation of clinical trials assessing prostate radiation therapy.

The purpose of this review is to communicate the current availability, content, and validation of acute and late radiation toxicity scales as well as relevant HRQoL instruments as it applies to prostate cancer radiation therapy. Instruments such as the International Prostate Symptom Score (IPSS) or the Sexual Health Inventory for Men (SHIM) that are not specifically designed for prostate cancer (but still have relevance in prostate cancer decision-making or side-effects) are not included in this review. It is hoped that this article can serve as a reference for researchers in the design of clinical trials and for clinicians in the interpretation of clinical studies involving the topic of prostate cancer.

Acute radiation toxicity scales

The Radiation Therapy Oncology Group (RTOG) has previously developed acute radiation toxicity scales for use in clinical trials and for clinician/researchers to use in communication of treatment toxicity. In terms of prostate cancer, the RTOG acute toxicity scale considers

effects on the lower gastrointestinal (GI) system and genitourinary (GU) system, Table 1. No sexual acute toxicity system exists in the RTOG schema.

Late radiation toxicity scales

The first internationally accepted late radiation toxicity scale was produced as a collaborative effort between the RTOG and the European Organization for the Research and Treatment of Cancer (EORTC). This late radiation toxicity scheme grades 17 different late tissue morbidities on a 0 to 4 scale in an analogous manner to the acute toxicity scales.[7] These scales were developed for use in all radiation treatment scenarios (i.e. not exclusive to prostate cancer). There is no sexual late toxicity scale; however, large intestine and bladder scales exist, Table 1.

In 1995, the Late Effects Normal Tissue Task Force Subjective, Objective, Management, and Analytic (LENT-SOMA) system was developed as a potential successor for the RTOG/EORTC scales.[8,9] The LENT-SOMA scale allows for the acquisition of data relevant to late toxicity by up to four different methods. The subjective method is a patient-related assessment, objective is a clinician-based assessment, management is based on steps taken to address the symptoms, and analytic is an investigation-based assessment of tissue toxicity. Each component is graded on a 4-grade scale (1-minor, 2-moderate, 3-severe, 4-irreversible/major intervention). No grade 5 (death or organ loss) toxicities are included in the LENT-SOMA scales. A total LENT score is generated by a mathematical relationship for each individualized toxicity scale. Rectal, bladder, and male sexual dysfunction LENT-SOMA scales exist within the schema.

Neither the RTOG/EORTC scale nor the LENT-SOMA scale completely reflects the scope of toxicity that can occur with prostate cancer therapy. For

TABLE 1. **Acute and late RTOG toxicity scales**

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
RTOG Acute Lower GI	no change	increase frequency/ quality of bowel habit with no medication requirement, discomfort not requiring analgesics	diarrhea requiring medications, mucous discharge not requiring pads/ diapers, pain requiring analgesics	diarrhea requiring parenteral support, mucous/blood discharge requiring pads/diapers, abdominal distention with radiologic distended bowel loops	acute/subacute obstruction, fistula, perforation, GI bleeding requiring transfusion, abdominal pain/tenesmus requiring tube decompression or bowel diversion
RTOG Acute GU	no change	frequency/nocturia twice pretreatment levels, dysuria/ urgency with no medication	frequency/nocturia less than hourly, dysuria/urgency/ spasm requiring local anesthetic	frequency/nocturia more than hourly, dysuria/urgency/ spasm requiring narcotics, gross hematuria	hematuria requiring transfusion, obstruction, ulceration, necrosis
RTOG Late large intestine	no change from baseline	slight epithelial atrohphy/minor telangiectasia (microscopic hematuria)	moderate frequency/ generalized telangieclasia/ intermittent macroscopic hematuria	severe frequency and dysuria, severe generalized telangiectasia, frequent hematuria, reduction in bladder capacity (< 150 cc)	necrosis/contracted bladder (< 100 cc), severe hemorrhagic cystitis
RTOG Late bladder	no change from baseline	mild diarrhea, mild cramping, bowel movement 5x daily, slight rectal bleeding or discharge	moderate diarrhea and colic, bowel movement > 5x daily, excessive rectal mucus or intermittent bleeding	obstruction or bleeding requiring surgery	necrosis, perforation, fistula

RTOG = Radiation Therapy Oncology Group

instance, neither assesses the requirement for multiple fulgurations due to rectal bleeding. The RTOG/EORTC scale does not assess the requirement of transfusion due to chronic rectal bleeding. Therefore, a modification to the LENT-SOMA scale (the Fox-Chase (FC) modification) which included one blood transfusion or more than two fulgurations as a grade three toxicity have been proposed.[10] The rate of grade three/four GI toxicity from high-dose RT for prostate cancer can range from 1%-6% depending on the definition of the late toxicity scale (RTOG – 1%, LENT-SOMA – 2%, FC-LENT-SOMA – 6%). The Fox-Chase modification for the late toxicity assessment of prostate cancer radiotherapy has been subsequently used in the setting of dose-escalation clinical trials.[3]

Composite acute and late toxicity scales

The National Cancer Institute Common Toxicity Criteria (NCICTC) is the most commonly used cancer related toxicity grading system in use.[7] Currently, version 3.0 is used for the assessment of surgery, chemotherapy and RT related toxicities in a single combined system. Hundreds of individual items are organized in 28 categories within the NCICTC with over 100 being relevant to RT effects. Of relevance to prostate cancer, the following acute and late toxicities are included in the system.

1. general: fatigue
2. GI: abdominal pain, colitis, diarrhea, fistula, hematochezia, proctitis
3. GU: dysuria, bladder spasms, hematuria, fistula, incontinence, obstruction, frequency/urgency, retention
4. sexual: impotence, infertility, and libido

All scales are graded on a five-point scale with 0 either representing no symptoms or no change in symptoms. In general, Grade 1 is mild toxicity, grade 2 is moderate, grade 3 is severe and grade 4 toxicity is disabling/life threatening. By definition, grade 5 toxicity is death attributable to a specific symptom.

Modular prostate cancer HRQoL scales

The FACT-P© prostate cancer specific instrument is a modular questionnaire that is administered in conjunction with the Functional-Assessment of Cancer Therapy – General (FACT-G©) general cancer questionnaire.[11-13] The version 2 FACT-G© (used in the FACT-P© study) is a 33-item instrument with physical, social/family, emotional, relationship with doctor, and functional well-being subscales.[14] The FACT-P© consists of a 12-item instrument that assesses constitutional symptoms, pain/discomfort, sexual/erectile function, bowel and urinary dysfunction. The combined FACT-G©/FACT-P© has one overall scale and five overlapping subdomains (physical, social, relationship with MD, emotional, functional). Raw scores are generated from the instrument and written and SAS® scoring guides are available. The published internal consistency ranged from 0.65-0.69. The FACT-P© was also able to discriminate patients by disease stage, performance status, and PSA. The FACT-P© was also shown to be responsive to change. It has the advantages of brevity, reliability, and validity; however, the FACT-P© assesses both systemic and local toxicities of treatment. This instrument may therefore be limited by non-specificity (systemic versus local symptoms) of what the instrument is measuring. As many patients can receive combination radiation therapy and androgen deprivation (AD), the side effects of AD such as fatigue and anemia can be assessed using the FACT-An module.

The first attempt at constructing a prostate cancer module to be used with the EORTC QLQ-C30© HRQoL general cancer questionnaire was described in 1996.[15] The EORTC QLQ-C30© is a multi-item and multidimensional instrument with five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, nausea/vomiting, and pain), and six individual items (dyspnea, insomnia, appetite, constipation, diarrhea, and financial).[16,17] A final 19-item prostate cancer instrument was constructed to cover areas relevant to treatment toxicities in the sexual, bowel, and urinary domains. Internal consistency of the sexual (alpha = 0.89), urinary (0.83), and bowel (0.77) subscales were found to be acceptable. Validity was also assessed by cross-correlation analysis with the subscales of the QLQ-C30© questionnaire. Moderate correlations (0.12-0.51) between the QLQ-C30© and prostate cancer module subscales demonstrated construct validity. In follow-up to the 19-item questionnaire, a new 25-item (PR25) instrument has been developed and is currently undergoing international field-testing. Scores are linearly transformed to a range from 0 to 100. However, similar to the FACT-P©, the focus of the new EORTC PR25 is for evaluation of both patients with metastatic and non-metastatic tumors.[18] The PR25 instrument incorporates the effects of hormonal therapy within the instrument question set. Data regarding the discrimination of groups and responsiveness of the new instrument is still pending.

Prostate cancer general HRQoL scales

Validation of the University of California at Los Angeles (UCLA) Prostate Cancer Index was reported in 1998.[19] It is a 20-item instrument that assesses impairment in sexual, bowel, and urinary domains. Six HRQoL scales (sexual symptoms and bother, urinary symptoms and bother, bowel symptoms and bother) were created and psychometrically assessed. All scales were linearly transformed to a scale from 0 (low HRQoL) to 100 (high HRQoL). Internal consistency ranged from 0.65 to 0.93. Test-retest reliability ranged from 0.66 to 0.93. Validity was assessed by documenting cross correlation of UCLA scales with analogous established scales and by assessment of concurrent validity (prostatectomy versus radiation toxicity differences). No information on responsiveness to change is available on this instrument.

The UCLA Prostate Cancer Index was expanded to a 50-item Expanded Prostate Index Composite (EPIC) instrument.[20] EPIC domains included summary subscales (urinary, bowel, sexual, and hormonal), and separate symptom and bother scale for urinary, bowel, sexual, and hormonal domains. Scores are linearly transformed into a 0 to 100 scale; and a SAS® macro is available on the company website (http://roadrunner.cancer.med.umich.edu/epic/epicmain.html) for scoring of the instrument. Internal consistency and test-retest reliability was above 0.80 for all summary scores and most specific scores. Validity testing was performed by assessing cross-correlation with the SF-12, FACT-P©, and American Urological Association Symptom Index (AUA-SI).[21] A short form of the EPIC questionnaire (EPIC-26) is also available to be administered in conjunction with the SF12 v2 and the AUA symptom scores. This instrument has been shown to have the ability to discriminate between different groups of individuals in a cross sectional survey of patients receiving brachytherapy, external-beam radiation therapy and radical prostatectomy. In addition, the EPIC instrument has been also been shown to be responsive over time in the post-prostatectomy setting.

The Prostate Cancer Quality of Life (PCQoL) instrument was developed to assess urinary, bowel, and sexual symptoms, bother and limitations.[22] An additional scale assessing "cancer worry" was included. Linearly transformed scores from 0 to 100 are generated from this instrument by means of a non-computerized calculation algorithm. Reliability and validity testing involved a total of 540 patients. Internal consistency ranged from 0.70 to 0.90 with reliability intraclass correlation (test-retest) coefficients of 0.59 to 0.92. The PC-QoL questionnaire was found to have good internal consistency, test-retest reliability, convergent and discriminant validity. In addition, the PC-QoL domains were found to have significant correlations with other prostate cancer, general health-related, and other global measures of HRQoL. Pilot testing in an outpatient clinical setting was also performed. The questionnaire was subsequently field-tested and was found to be a feasible self-administered questionnaire in an outpatient urology setting. No information on discrimination of groups or on responsiveness of change over time is available on this instrument.

Prostate cancer radiation treatment HRQoL scales

A 43-item acute radiation toxicity questionnaire in the urinary, bowel, and sexual domains has been developed in Sweden.[23] Internal consistency was above 0.70 for all domains. The test-retest intraclass correlation coefficient was above 0.60 for all domains. Inter-rater reliability (between patient and doctor/nurse) was 0.60 as measured by the intraclass correlation coefficient. The questionnaire was able to detect acute changes during radiotherapy (responsiveness). Late effects were not studied as part of this instrument.

An additional 31-item late toxicity instrument with six subscales including urinary (urgency and stream strength), sexual (interest/satisfaction and impotence), and bowel (daily living and urgency) was developed in Chicago.[24] Raw scores of between 0-18 were generated from the instrument and no details regarding scoring mechanisms were included in the report. Internal consistency ranged from 0.48 to 0.92. No test-retest reliability was performed. Reported validation procedures did not involve external construct validity and only used patient retrospective evaluation of symptom "bother" in order to provide validation. No information on responsiveness is available.

Recently, construction of a short 29-item self-administered questionnaire with genitourinary, gastrointestinal, and sexual symptom and bother items was performed.[25] The instrument uses scaled scores ranging from 0-100 and a both non-computerized scoring guide and a SAS® macro are available. A pilot study (n = 37) demonstrated that the Prostate Cancer Radiation Toxicity (PCRT) questionnaire was comprehensive (94%) and easy to administer (1.3% missing data) according to a global subjective assessment by patients. Item reduction and grouping (n = 100) resulted in three overall HRQoL scales: (a 4 item genitourinary scale Cronbach's alpha = 0.639, a 12 item gastrointestinal scale alpha = 0.859, and a 5 item sexual scale alpha = 0.700). Test-retest reliability was high and

(n = 274) demonstrated intraclass correlation coefficients (CC) of 0.811 (GU), 0.842 (GI), and 0.740 (sexual). Discriminant validity analysis (n = 274) demonstrated Pearson CC of 0.449 (GU-GI), 0.200 (sexual-GU), and 0.09 (sexual-GI), which suggested that the various scales measured different constructs. Content validity analysis (n = 274) demonstrated significant correlations between analogous subscales between PCRT and the PCQoL (range 0.35-0.78). Smaller correlations exist between the PCRT and general HRQoL and health questionnaires such as FACT-G (0.19-0.39) and SF-36 (0.03-0.34). The questionnaire has been used to discriminate between groups of individuals having different treatment. The validation of the PCRT in terms of acute toxicity, post-operative radiation therapy, and the assessment of changes over time (responsiveness) is ongoing.

Conclusion

A variety of prostate cancer acute/late toxicity scales, modular and non-modular prostate cancer instruments, and three RT prostate cancer questionnaires have been reported in the literature. These scales and instruments vary in terms of domain content, level of validation, and general acceptance in the oncology community. The choice of which HRQoL instrument to use will depend on a comparison of the research question that is being asked with the domains/items within the questionnaire. Investigators should familiarize themselves with these instruments in terms of content, scoring procedures, and validation procedures prior to implementing a HRQoL instrument. Whether or not a questionnaire has been validated to discriminate between groups or to assess

TABLE 2. **Selected ongoing clinical trials assessing toxicity and health-related quality-of-life**

Trial	Research question	Patient population	Sample size	Primary outcome	HRQoL outcomes
RTOG 0415	A randomized phase III non-inferiority clinical trial assessing hypofractionated radiation of 70 Gy in 28 fractions to the prostate versus standard fractionation of 73.8 Gy in 41 fractions	Low-risk prostate cancer	n = 1067	Disease-free survival	CTCAE v3 EPIC EQ-5D (utility) HSCL-25 (anxiety/ depression)
RTOG 0126	A randomized phase III superiority clinical trial assessing dose-escalated radiation of 79.2 Gy in 44 fractions versus standard fractionation of 70.2 in 39 fractions	Intermediate-risk prostate cancer	n = 1520	Overall survival	CTCAE v3 IIEF (erectile function) FACE (GI) Switzer (utility)
OCOG PROFIT	A phase III randomized study assessing the relative efficacy of dose-escalated radiation therapy (78 Gy in 39 fractions) versus a hypofractionated course of radiation (6000 Gy in 20 fractions)	Intermediate-risk prostate cancer	n = 1204	Biochemical failure	RTOG acute/late toxicity
RTOG 0521	A randomized phase III relative efficacy assessment of 2 years of androgen suppression combined with radical external beam radiation therapy (72 Gy-75.6 Gy) plus or minus adjuvant docetaxel chemotherapy (six cycles, 75 mg/m^2 q21 days)	High-risk prostate cancer	n = 600	Overall survival	CTCAE v3
Ottawa tomotherapy trial	A phase III randomized relative efficacy comparison of three-dimensional conformal radiation therapy versus helical tomotherapy with 78 Gy in 39 fractions and three years of Eligard® Hormonal Therapy	High-risk prostate cancer	n = 72	Grade 2 late rectal toxicity	RTOG acute/ late toxicity EORTC QLQ-C30 EORTC PR25 PCRT

OCOG = Ontario Clinical Oncology Group; NCIC = National Cancer Institute Canada; HRQoL = Health-related Quality-of-life

responsiveness is an important factor when deciding on an instrument. In the opinion of the authors, the FACT-P and EPIC questionnaires have demonstrated strong psychometric properties of feasibility, reliability, validity, and responsiveness. Both questionnaires have clear scoring algorithms with the option of SAS® scoring macros. In terms of targeted prostate cancer radiation instruments, the PCRT has demonstrated good psychometric properties including discrimination between groups and a clear scoring algorithm with available SAS® macro. However, further validation of the PCRT is required prior to general implementation. Various studies are ongoing: post-operative setting, responsiveness in the post-RT setting, and cross-validation with the EPIC and QLQ-PR25 questionnaires. With increasing research and clinical activity in dose escalation, dose per fraction escalation, new radiation delivery technologies, and the integration of novel agents (chemotherapy and potential molecular agents) with radiotherapy; the use of well-validated acute and late prostate cancer toxicity scales and HRQoL instruments continues to be a important part of the evaluation of the therapeutic ratio in prostate radiotherapy, Table 2. Appropriate selection and future standardization of instruments will hopefully result in the ability to identify pertinent adverse events and to compare outcomes between clinical trials in a reliable and valid manner. □

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