Title: "Prospective Evaluation of Gastrointestinal and Genitourinary Side Effects of Pelvic Radiotherapy: Association Between Patient-Reported Outcomes and Clinician-Reported Outcomes with A View to Improving Quality of Care"

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ABSTRACT

Background: Patients undergoing pelvic radiotherapy (RT) frequently develop acute gastrointestinal (GI) and genitourinary (GU) toxicities during treatment [1]. Most studies on toxicities have used clinician-reported outcomes (CROs) for reporting intra-treatment assessments. Recent research shows that patient-reported outcomes (PROs) better capture the quality-of-life (QoL) issues that patients care about [2].

Objectives: This study aims to evaluate the feasibility of collecting PROs and CROs for GI/GU toxicities in a busy tertiary care cancer centre and assess their concordance. Secondary objectives include the exploration of the influence of baseline characteristics on treatment-related toxicity and determining the utility of PROs to predict adverse health measures, such as hospitalizations or medication changes.

Hypothesis: We hypothesized that collecting digital PROs is feasible and that there will be discordance between PROs and CROs when assessing GI/GU toxicities of pelvic RT.

Methods: All patients receiving curative pelvic RT for the first time at the McGill University Health Centre Radiation Oncology clinic were eligible. Through a mobile application (Opal), patients completed validated electronic PRO questionnaires on acute GI/GU toxicities and QoL. These questionnaires were administered at baseline, after each treatment session, at two weeks, and at six-month follow-up visits. The treating physician filled in the traditional intra-treatment forms simultaneously.

Results: 102 patients were included. Patient reporting of frequent toxicities (diarrhea, frequency, and dysuria) was markedly higher, with only slight to fair agreement with CROs (p-value <.001 in both Somer's D and Macnemar-Bowker's tests). On stratified analyses, there was little evidence of an association between reported symptoms and baseline characteristics. Also, we

couldn’t detect any statistically significant association between reported outcomes and specific adverse health measures, such as hospitalizations or medication changes.

Conclusion: The high completion rate of the digital questionnaires confirms the feasibility of collecting digital PROs in a busy tertiary care clinic. The weak agreement of PROs with CROs suggests that PROs complement CROs in evaluating patient symptoms during and after pelvic radiotherapy. The **s**tudy findings support the creation of a new algorithm that includes both patient and clinician input. Physicians can positively influence patients' QoL by anticipating problems and toxicities that require additional care.

RÉSUMÉ

Contexte : Les patients qui subissent une radiothérapie pelvienne (RT) développent fréquemment des toxicités gastro-intestinales (GI) et génito-urinaires (GU) aiguës au cours du traitement [1]. La plupart des études sur les toxicités ont utilisé les résultats rapportés par les cliniciens (CROs) pour rapporter les évaluations intra-traitement. Des recherches récentes montrent que les résultats rapportés par les patients (PROs) reflètent mieux les questions de qualité de vie (QoL) auxquelles les patients sont attachés [2] .

Objectifs : Cette étude vise à évaluer la faisabilité de la collecte des PROs et des CROs pour les toxicités GI/GU dans un centre de cancérologie tertiaire très fréquenté et à évaluer leur concordance. Les objectifs secondaires comprennent l'exploration de l'influence des caractéristiques de base sur la toxicité liée au traitement et la détermination de l'utilité des PRO pour prédire les mesures de santé défavorables, telles que les hospitalisations ou les changements de médicaments.

Hypothèse : Nous émettons l'hypothèse qu'il est possible de collecter des PRO numériques et qu'il y aura une discordance entre les PROs et les CROs lors de l'évaluation des toxicités GI/GU de la RT pelvienne.

Méthodes: Toutes les patientes recevant une RT pelvienne curative pour la première fois à la clinique de radio-oncologie du Centre universitaire de santé McGill étaient éligibles. Par le biais d'une application mobile (Opal), les patientes ont rempli des questionnaires électroniques validés sur les toxicités GI/GU aiguës et la qualité de vie. Ces questionnaires ont été administrés au début de l'étude, après chaque séance de traitement, après deux semaines et lors des visites de suivi à six mois. Le médecin traitant a rempli simultanément les formulaires intra-traitement traditionnels.

Résultats : 102 patients ont été inclus. Le nombre de toxicités fréquentes (diarrhée, fréquence et dysurie) rapportées par les patients était nettement plus élevé, avec une concordance faible à moyenne avec les ORC (valeur $p < 0,001$ dans les tests de Somer's Det de Macnemar-Bowker). Les analyses stratifiées n'ont pas mis en évidence d'association entre les symptômes déclarés et les caractéristiques de base. De même, nous n'avons pas pu détecter d'association statistiquement significative entre les résultats déclarés et des mesures de santé défavorables spécifiques, telles que les hospitalisations ou les changements de médicaments.

Conclusion : Le taux élevé de remplissage des questionnaires numériques confirme la faisabilité de la collecte des PROs numériques dans une clinique de soins tertiaires très fréquentée. La faible concordance entre les PROs et les CROs suggère que les PROs complètent les CROs dans l'évaluation des symptômes des patients pendant et après la radiothérapie pelvienne. Les résultats de l'étude soutiennent la création d'un nouvel algorithme qui inclut à la fois les données du patient et celles du clinicien. Les médecins peuvent influencer positivement la qualité de vie des patients en anticipant les problèmes et les toxicités qui nécessitent des soins supplémentaires.

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PREFACE & CONTRIBUTIONS OF AUTHORS

This thesis was written following the manuscript-based thesis guidelines. I am the first author to present the substantive contribution of my work. I performed the literature review, the methods and design, analyzed and interpreted the data, and wrote the manuscript. I also prepared for the submission to a peer-reviewed journal. I am targeting the “Radiation oncology” journal.
Dr. Alfieri helped with the study design, statistical analyses, interpretation of data, and critical revision and editing of the thesis and manuscript for important intellectual content. Dr. Souhami and Dr. Hijal helped develop and interpret the results and critically reviewed the study. Dr. Talía Malagón helped in developing the statistical design and results interpretation. All authors will approve the final manuscript before submission to a journal and will agree to be accountable for all aspects of the work before final publication in the scientific literature.

LIST OF ABBREVIATIONS

Body Mass Index (BMI)

Common Terminology Criteria for Adverse events (CTCAE)

Clinicians reported outcomes (CROs)

Emergency room (ER)

European Organisation for Research and Treatment in Cancer (EORTC)

Food and Drug Administration (FDA)

Gastrointestinal (GI)

Genitourinary (GU)

Inflammatory bowel disease (IBD)

Patient Reported Outcomes (PROs)

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

Quality of life (QoL)

Radiotherapy (RT)

INTRODUCTION AND LITERATURE REVIEW

PATIENT-REPORTED OUTCOMES (PROs)

Development and Importance

Cancer outcomes such as survival estimates and clinician-reported treatment toxicities have traditionally been the measures of treatment outcomes. Advances in modern medicine and the growth of evidence-based medicine have made dramatic progress in oncology regarding the availability of treatment, quality of care, and survival. Simultaneously, the doctor-patient relationship has also changed dramatically [3]. Patients' preferences, choices and needs have been positioned at the core of the decision-making process because patients' feelings influence therapeutic decisions, patient satisfaction, and quality of life during and after the treatment [3-7]. The attention to patients' subjective perspectives has led researchers to recommend the use of interpretative research methods that can directly explore topics such as barriers in help-seeking [10], doctor-patient communication [11] and the needs of families and patients [12]. This patient-oriented approach should be capable of capturing the dual component of every medical act: the care and the cure [4, 7]. Accordingly, the past decade has been characterized by a movement from a doctor-centred to a patient-centred approach, in which doctors seek to see the illness through their patients' eyes [8].

This new context has guided the emergence of PROs; PROs are additional indicators that come directly from the patient. PROs provide patient perspectives on treatment effects beyond survival, disease, and physiological markers: they are often the outcomes most important to patients [9, 10].

There is emerging evidence that PROs are helpful as communication tools to improve symptom control, assist in the early detection of adverse events [11-16] and treatment effect monitoring in

the oncology setting [17-19], as well as to enhance physician-patient communication [19, 20]. In addition to adding value to patient care in the clinic, recent findings have also reported the impact of PRO monitoring on broader indicators, including overall survival and reduced emergency department visits [21-24].

However, evidence demonstrates that clinician and patient perspectives on health status do not necessarily align [13, 25, 26]. Clinicians often inaccurately perceive and underestimate the incidence and severity of patient symptoms [27]. The evidence demonstrates that clinicians miss about half of their patients' symptoms during treatment [12, 28]. This is mainly because standard medical examinations and investigations obtain patient physical and biomedical data, but such means cannot capture information about the patient's psychosocial function and perceived well-being (e.g. symptom severity, distress and QoL) [7]. Consequences of missing symptoms include patient suffering due to poor symptom control, missed treatments, emergency department visits, and hospitalizations. Indeed, poorly controlled symptoms are the principal driver of preventable emergency department visits, such as pain, shortness of breath, dehydration, nausea or vomiting, diarrhea, and fatigue [29, 30].

Moreover, studies have shown that oncologists act according to what they believe is best for the patient, attempting to balance hope and uncertainty, often resulting in collusion and false optimism [31]. Overall, the literature shows a divergence between the perspectives of doctors and patients about cancer management—a divergence that leaves patients' needs significantly unaddressed [32]. Multiple studies show that systematic consideration of patient-reported symptoms closes this gap, enhancing patient-clinician communication, clinician recognition and management of symptoms [33, 34].

Definitions

PROs are becoming an essential component of health outcome assessments for understanding cancer care and the effect of cancer on people's lives [17, 35]. According to the Food and Drug Administration (FDA), PRO is «A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's response by a clinician or anyone else» [36]. Likewise, the European Medicines Agency defines a PRO as «any outcome evaluated directly by the patient himself and based on patient's perception of a disease and its treatment(s)» [37].

Application

PROs are increasingly being utilized as a part of the clinical encounter to guide treatment decisions and determine intervention effectiveness [38, 39]. PROs should measure a *relevant and experienced concept* by a patient. Most broadly, PROs include concepts such as symptoms [40], patient functioning [41], and patient satisfaction with or perceptions of care. Another concept is health-related QoL, which is the patient's subjective perception of the effect of his disease and its treatment on daily life, physical, psychological, and social functioning and well-being [42]. The concept can be evaluated in absolute terms, such as pain severity at a specified time or change from a previous measurement [43].

PROs have several wide-reaching applications. They are used in randomized clinical trials, cohort studies, and comparative effectiveness research to measure the effect of medical intervention on one or more concepts [44]. PROs also have an increasing role in Health Technology Assessment decision-making, especially in the UK (National Institute for Clinical Excellence), France (Transparency Committee) and Germany (Federal Joint Committee) [45]. In the clinical setting, guidelines for symptom care from leading organizations like the American

Cancer Society, The National Comprehensive Cancer Network, and the United States Agency for Healthcare Research and Quality recommend using PROs for assessment due to the subjective nature of symptoms [46-50].

Instruments

The measurement of symptoms is crucial for understanding the burden of cancer because uncontrolled symptoms could increase mortality in patients with cancer. Although the Common Terminology Criteria for Adverse events (CTCAE) is a standard method for clinicians grading adverse effects, additional assessment from the patient perspective is valuable since about 10 % of the toxicities listed in the CTCAE are subjective and can be best evaluated by collecting information directly from the patient perspective [51]. A recent systematic review verifies that clinicians often underestimate the incidence, severity and stress of the symptoms experienced by cancer patients [26]. The FDA and others have acknowledged that patients are best positioned to report their symptoms [52].

There is no record of all valid and reliable PROs instruments currently in use; several PROs databases exist listing thousands of PROs instruments, and new instruments are continuously being developed. [45, 53].

A PROs instrument can comprise a single question (item), such as a pain Numerical Rating Scale or can have many items grouped to form a total score and/or domain scores, e.g. the European Organisation for Research and Treatment in Cancer (EORTC) QLQ-C30 [45].

PROs instruments can be general or specific to the patient's cancer type, stage of disease, treatment, or phase of survivorship [53, 54]. Domains assessed may include but are not limited to, physical, emotional, psychological, social and overall QoL [55].

Generic PROs instruments can be applied to the general population or across various diseases. This facilitates comparison to societal norms and between disparate groups of patients. Such measures are usually multidimensional, describing many areas of life. A good example of the most commonly used generic measures is the Medical Outcomes Short Form 36 (SF-36) [42]. However, generic measures may be unidimensional (e.g. Female Sexual Function Index) [56]. Disease-specific PROs instruments have been created for use in particular patient populations. This may be generally defined, e.g. the EORTC QLQ-C30 (core questionnaire) [57] for use with cancer patients in general. Broad disease-specific measures often also have built-in modules where many forms of the disease exist, e.g., the EORTC lung cancer module [58].

The most common PROs approach for oncology has been to assess the broad multidomain concept of health-related QOL using instruments built in a different therapeutic era [59-61]. These existing QOL measures have advantages, including validated translations across multiple languages and familiarity with their use in the cancer research community. Many instruments have also been extended to include disease-specific modules to better capture disease- and treatment-related symptoms [62, 63]. However, although the PROs instruments commonly used in oncology trials address a broad range of essential symptoms and functional domains, they usually include the same questions regardless of disease stage or the therapy under study. This can result in questions that may be less relevant to the trial context and/or miss the evaluation of essential symptoms (e.g., toxicities not currently included in existing static instruments) [64]. More recently, the National Quality Forum has initiated the development of quality metrics that use PROs, such as pain [65]. Several publications have provided in-depth guidance regarding the use of PROs in clinical practice [47, 49, 66], quality assessment [65], and research [43, 67, 68].

Format

Participant engagement is a vital aspect of any clinical research. The method of data collection used throughout the study is essential to ensure data collection quality, reliability, and validity. In addition, it must be cost-effective for participants, funding organizations, and researchers [69-71].

Patient-reported outcome measures can be administered by self-report, interviewer-administered or proxy-report. A self-report PROs is completed by the patient directly. When possible, self-report administration is considered the gold-standard of PROs data collection because data are collected from the patient directly [94]. PROs are collected via standardized questions administered in a variety of ways [9], including paper, electronic (e.g., online, tablet, mobile phone or laptop) or telephone Interactive Voice Response System (IVRS) [53, 72].

Digital PROS

With the ambition of providing more person-centred care at a lower cost, patients are increasingly expected to contribute to their care by sharing health-related information through digital and networked technology. This movement is sometimes called 'the personalization of medicine' [73]. With personal digital technologies and digital health infrastructures reaching beyond the clinical setting and into patients' homes, patients invest effort in producing health data. This has implications for the produced data and the patients themselves [74].

Formerly, PROs tools were primarily applied in research at an aggregate level to account for patients' experience with healthcare delivery. However, when used in clinical practice, PROs tools increasingly target the individual level [75], inviting patients to respond to digital questionnaires about physical and psychosocial well-being. This is done to improve communication between patients and healthcare professionals as part of clinical decision-making

and can be used as a tool for triage. Thus, PROs tools are applied in the clinic before a consultation to inform clinicians and ensure a more purposeful consultation, or in patients' homes remotely eliminating the need for clinic visits [76]. Recommendations for collecting PROs in adult oncology emphasize the need for electronic data capture technologies [67].

A considerable number of studies of PRO measures have assessed the equality of paper vs. screen-based (e.g., tablet, laptop/desktop computer, small handheld device) administration across many populations, and meta-analyses confirm high levels of reliability when comparing paper-based and screen-based administration [77, 78]. Tablet computers have the potential to facilitate the collection of PROs in the clinic setting. Tablet computers offer mobile, secure, reliable, wireless data collection, instantaneous data storage, and nearly immediate data availability, with easy-to-use software controls that are operated by a touchscreen. Wireless data collection provides enhanced security because patient-reported data are never stored on the device [79]. Tablet computer screens are also much easier to clean and disinfect than the mice and keyboards of desktop/laptop computers, which are significant reservoirs of pathogens compared to other user interfaces [80].

Mobile phone technology has been progressively used to promote health-related behavioural change and self-management of care via apps and automated SMS text messages [81-83]. However, a Cochrane review explicitly looking at mobile phone apps as a data delivery method for self-administered questionnaires observed that none of the included studies in the review reported data accuracy or response rates [84]. Furthermore, a systematic review of studies using mobile phones for data collection revealed that they were built on very small sample sizes, collected intermittent data, or had limited longitudinal data collection [85-88].

Although former studies have compared traditional paper-based data collection with data collection using mobile phones [111, 112], there is limited evidence measuring the efficiency of a combination of paper or email-based methods compared to mobile phones as part of an automated data collection management system. There is also limited evaluation of electronic data collection into a streamlined data managing system. [89]. Integration and evaluation of mobile phone research management systems that are cost-effective, efficient, and acceptable to both researchers and patients are essential, given the increasing use of mobile phone technology [90] and the high costs of undertaking research [91].

Barriers

Despite the clear benefits, integration and use of results of PROs in oncological care are lacking [92] as the routine implementation of PROs in the clinic faces many challenges [93-95]. These challenges extend from administrative to technical and workflow issues [96, 97].

First, there are concerns with choosing a valid and reliable PRO measure, which is a questionnaire or tool that analyses individual patient perceptions of their health and health-related experiences and outcomes [17, 98, 99]. A comprehensive approach is required to design, analyze and interpret results [100-103].

Missing data due to incomplete PROs (i.e., one or more unanswered questions) or uncompleted PROs (i.e., the entire questionnaire is unanswered) can limit generalizability or introduce biases in analyses and the resulting conclusions or recommendations [104]. Lower completion rates can have downstream consequences on health because clinicians and researchers cannot assess outcomes in these populations in a comprehensive manner [18, 35, 105-110].

Even when PROs are fully completed or when completion rates are high, data validity depends on comprehension and patients' ability to select responses that accurately reflect their

experiences [96]. Furthermore, PROs completion challenges are not experienced uniformly across the patient population, with one study finding lower completion rates in patients who were older than 75 years, Hispanic, or black, or had Medicare or Medicaid in the US [111].

On the patient's side, gathering PROs may add an undue burden on patients who do not understand the importance of PROs or have low literacy skills [112]. A recent study found nine related but distinct factors: questionnaires' platform layout, print literacy, health knowledge, technology knowledge, language proficiency, physical functioning, vision, cognitive functioning, and time. Because some of these factors may affect minority and other disadvantaged populations at disproportionate rates, failure to address them may perpetuate existing health disparities among these communities. These factors must be addressed before capturing patient-reported health assessments in a comprehensive, equitable, and inclusive manner [148].

It is also essential to consider how to design and implement PROs in a fashion that resonates with highly skilled patients. Without consideration of high-skill patients' needs, they may experience frustration or lose interest or engagement, therefore also leading to lower quality participation and questionnaire completion. When discussing potential solutions for various barriers, the patients who did not experience those barriers were wary, citing concerns about making questionnaires unnecessarily longer or harder to navigate. This represents an opportunity to leverage emerging technology, such as mobile health technology, to create adaptable PROs administration platforms responsive to individual patient needs [91, 113].

From a clinician's point of view, frequent barriers to the implementation of PROs are lack of time, training and support and low personal confidence [114]. Clinicians may lack guidance in choosing suitable tools to capture concepts that are important to patients and clinicians [20, 95, 98]. In a recent study, only a quarter of the surveyed clinicians reported capturing PROs in

routine clinical practice. The implementation barriers to PROs use differ across respondents in various professions and levels of socioeconomic resources. Furthermore, most studies concentrate on reviewing experiences and implementation challenges in users of PROs, and little is known about the difficulties oncologists face [114, 115].

On a larger scale, technical and administrative challenges in creating a user-friendly platform for electronic data capture, linkage with relevant clinical characteristics, and data security worries also hinder the successful implementation of PROs monitoring in care delivery settings [18, 97, 116].

On an organizational level, resources and strategies for effective implementation are often missing [95]. Other system-level challenges include problems assimilating the use of PRO information into clinical workflows [18, 19, 117] and weaknesses in the expertise needed to interpret PRO data and apply the information to clinical decision-making [118-120].

Few studies have relatively assessed patterns of PROs adoption in cancer clinical practice in different regions of the world. For example, most PROs have been developed in high-income settings, and their applicability in low-resourced settings may be limited [97].

Understanding all these barriers is crucial, as successful adoption and sustainable adoption of new practices, such as routine PROs collection, need to be compatible with stakeholder needs and values and impose minimal burden on them [35, 121, 122]**.**

RADIOTHERAPY (RT)

Enhancing the QOL for patients with cancer both during and after treatment has been largely investigated [123, 124]. Multiple studies evaluated the use of PROs in patients undergoing chemotherapy. Comparatively, fewer studies have assessed the benefits of utilizing PROs in patients undergoing radiotherapy despite often having extended treatment courses[125].

Radiotherapy is a locoregional treatment used for the radical cure of tumours in their early stages with high success rates in the absence of metastatic spread. It is the most important non-surgical treatment in cancer management [126]. The main drawback of radiotherapy is the fact that it affects both cancer and healthy cells located in the tumour area. Although advances in radiotherapy have allowed more accurate delivery of radiation to the tumour and the avoidance of surrounding tissue exposure, the effects of this type of therapy on healthy tissues have not been eliminated [127-133]. Most cancers treated with radiotherapy are in the lower abdomen and pelvis, which is why complications often involve the gastrointestinal tract and the urinary tract. The most common pelvic tumours requiring radiotherapy include prostate, rectal and anal cancer in men and cervical and endometrial cancers in women. Other tumours that cause gastrointestinal and urological complications after radiation include bladder, testicular, urethral, ovarian, vulvar, and vaginal cancer [133-138].

Normal tissues surrounding the tumour will be exposed to radiation during radiotherapy, like the rectum, sigmoid, small bowel, urethra, and bladder, which are in close physical proximity to the tumour. Due to the anatomy of these areas, gastrointestinal and urological complications occur after radiological treatment of malignancies of the genitourinary and digestive systems [139, 140]. Radiation toxicity affects a considerable proportion of patients, significantly reducing their quality of life and adding an extra burden on the cost of health care. Symptoms can appear in the acute phase or after several months to years. Symptoms are deemed "acute" if they occur within treatment or up to 90 days after treatment. These are usually reversible [130, 134, 141-143].

Although severe intestinal and genitourinary damage is less common with the introduction of innovative radiotherapy planning and delivery methods, a less severe degree of toxicity is common [3-5]. Radical treatments to cure cancer will cause side effects. They are not due to medical error

or poor judgement, and to a certain degree, they are inevitable. However, they are not always acknowledged or assessed accurately, and clinical trials to modify toxicities are often not prioritized [144].

Risk Factors for Pelvic Radiation Toxicity

Pelvic radiation toxicities commonly occur following external beam therapy. Several patients and treatment-related risk factors have been shown to influence the pathophysiology of radiation toxicity, although the exact effects of these factors are still to be defined. A better knowledge of the pathophysiology of radiation toxicity may provide the opportunity to develop more effective preventive and therapeutic strategies [145, 146].

Therapy-Related Risk Factors

Radiation dose, fractionation, and field size

The degree of injury to healthy tissues varies according to tissues' radiosensitivity, the radiation doses and the irradiated volume, the dosing intervals, and the delivery method [127, 132, 133]. Some of these factors are adjustable, allowing the protection of normal tissues against injury.

Combined modality approaches

Combined modality therapy raises the risk of radiation toxicity. Previous surgery or concurrent chemotherapy is associated with an increased radiation toxicity incidence [147].

Patient-Related Risk Factors

It was once thought that the radiation dose was entirely responsible for the damage that developed, but patient-related factors are increasingly important. Yet little effort has been extended to quantify the degree of risk from these factors for any one individual [148].

Patient factors and individual variations

Individual patient phenotypic factors have been found to influence the vulnerability to intestinal radiation toxicity. It was suggested that older patient age is associated with an increased risk of developing reduced organ function after radiotherapy [149-151]. Body habitus has been reported as another predisposing factor; elevated body mass index (BMI) has been shown to be correlated with increased interfractional displacement in a number of small studies of radiotherapy for prostate, abdominal and endometrial cancer [152]. Smoking status and previous history of surgery have been associated with the risk of intestinal toxicity [153-157].

Medical Comorbidities

- Vascular disease**:** Co-morbid vascular disorders such as hypertension, diabetes mellitus, and atherosclerosis predispose patients to increased vascular toxicity after radiation and subsequent intestinal wall ischemia and impaired tissue repair [158].
- Inflammatory bowel disease: Co-morbid inflammatory bowel disease (IBD) is sometimes considered a relative contraindication to radiotherapy for fear of greater acute and late side effects [159-161].
- Collagen vascular diseases increase the risk of acute and chronic radiation toxicity, as has been reported by Chon et al. [162] in 4 different trials in patients with and without Collagen vascular diseases. Also, radiation may cause an acute exacerbation of systemic symptoms in patients with Collagen vascular diseases [163], possibly through the release of fibroblast-triggering mediators by the inflammatory cells [162].

Symptoms Resulting from GI And GU Radiation Toxicity

The severity of toxicity is graded depending on the severity of different symptoms or clinical manifestations ranging from minor symptomatic changes to severe life-threatening complications. Multiple toxicity grading systems have been established to assess adverse events of cancer

treatment [164]. Generally, grade 1 and 2 radiation injuries are frequent, and they often require no treatment, although they can have a considerable effect on patient QoL. The Radiation Therapy Oncology Group [165] and the CTCAE grading system are examples of toxicity grading systems commonly used to evaluate radiation toxicity severity [164].

Small Intestine

The small intestine receives radiation during radiotherapy of pelvic or abdominal malignancies. A significant correlation has been suggested between the irradiated small bowel volume and the probability of acute toxicity irrespective of the radiation dose delivered [166]. Other predictors of acute small intestine toxicity include concurrent chemotherapy. This effect has been described in 186 cervical cancer patients who received 45 Gy preoperative pelvic radiotherapy alone, where 5% of patients suffered grade 3-4 toxicity compared to 14% of 183 patients who received radiotherapy and weekly cisplatin [167]. The fixed portions of the small intestine, such as the duodenum and the terminal ileum, are at increased risk of radiation toxicity as they are more susceptible to receiving higher doses of radiation than the mobile parts of the small intestine.

Nausea, vomiting and abdominal pain are early clinical manifestations occurring during the first two weeks following radiotherapy and may be caused by the release of inflammatory cytokines after irradiation. Diarrhea and abdominal pain occur during the first two weeks of radiotherapy for abdominal or pelvic malignancies in 20% to 70% of patients [168]. This may result from direct radiation toxicity to the small intestinal mucosa, causing epithelial atrophy and reduced mucosal blood flow [169]. The acute symptoms usually resolve within three weeks after radiotherapy [158]. The rate of severe small intestinal complications after radiotherapy for rectal cancer can vary significantly according to the tumour and treatment characteristics. Reports indicate rates of 0.8% to 13% for small intestinal obstruction [76, 84, 85] and 0.6% to 4.8% for intestinal

fistulisation [76, 86]. Patients with severe small intestinal toxicity have a poor prognosis as surgery to manage strictures is complex and has poor outcomes [169, 170].

Colon and Rectum

During pelvic radiotherapy, the colon and rectum are usually affected as their anatomical locations fall within the radiation field of various tumours. The fixed parts of the colon, the caecum and the rectum are at greater risk of receiving higher doses of radiation than the rest of the colon [171-173]. The data on the dose-volume effect in radiation-induced rectal toxicity was reviewed by Michalski et al. [174]. The incidence of greater than grade 2 toxicity from different studies was variable according to each study's dose, treatment parameters, and scale. Among the studies, an incidence from 13.5% to 16% was reported. Identified predictors for grade 2+ rectal injuries include the volume of the rectum irradiated and a total radiation dose > 60 Gy in 3-dimensional conformal radiotherapy. Concurrent chemotherapy has been studied in the European Organization for Research and Treatment of Cancer analysis, where participants received 45 Gy preoperative radiotherapy or radiotherapy and 5-fluorouracil (5-FU). Greater than grade 2 diarrhea occurred in 17% of the radiotherapy alone group compared to 38% of the radiotherapy and 5-FU group [175]. Acute radiation damage to the colon can be severe and, in 5%-15%, can result in therapy interruption or treatment plan alteration [176]. A previous study showed that 47% of women who received radiotherapy for cervical or endometrial cancer reported symptoms of radiation intestinal toxicity affecting the quality of life within three months following therapy completion [177]. These results are consistent with another structured questionnaire study [178], which showed that 53% of patients had reported bowel symptoms considerably affecting their quality of life, while 81% of patients described new-onset GI problems after receiving radiotherapy.

Patients suffer from various symptoms, such as abdominal pain and changing bowel habits with intermittent diarrhea. Fecal incontinence has been reported in up to 20% of patients and significantly reduces patients' quality of life [178, 179]. Unlike radiation toxicity to the small bowel, radiation toxicity to the colon does not compromise nutrient absorption, and malabsorption is uncommon [169].

Urinary Tract:

Radiation cystitis is a common complication of radiotherapy. It occurs in 5% to 10% of patients receiving pelvic radiation and most often occurs during prostate, bladder or cervical cancer treatment [133, 137, 180-182]. It can occur during or shortly after treatment. It manifests as dysuria, frequency, and urgency to urinate [183, 184]. However, acute radiation cystitis is common and usually self-limiting [181, 184]; it significantly affects patients' quality of life and can result in life-threatening situations [181]. Complications of radiotherapy constitute up to 7% of emergency admissions to the urology department [136]. The incidence of grade 3 acute GU toxicity ranges between 0% [185] and 12% [186] for doses ranging from 65 to 80 Gy. Both grades 1 and 2 acute GU toxicities range from 0% [187] to 75% [188] for grade 1 and 0% [187]to 54% [189] for grade 2. Grade 2 GU toxicity is mostly transient. Smoking, previous abdominopelvic surgeries, and diuretics significantly affect the occurrence of acute GU toxicity grade ≥ 2 [190].

ARE GI/GU SYMPTOMS AFTER PELVIC RADIOTHERAPY ADEQUATELY DOCUMENTED?

Although studies frequently report that 10-15% of patients develop moderate or severe GI toxicity, patient-focused research suggests these figures are a significant underestimate [141, 191]. The lack of toxicity reporting is exemplified in one systematic review of randomized trials highlighting inadequate reporting on the incidence of acute and late toxicity in treating patients with cervical

cancer [192]. In contrast, another assessing surgical treatment and outcomes highlighted a complete lack of randomized controlled trials [193].

Studies that have assessed 'symptoms causing moderate or severe distress' or whether their symptoms prevent them from doing things regularly in patients suggest that if radiotherapy was part of their treatment, one-third of patients would be left with significant GI dysfunction [104]. Although there is a risk of bias in some of these studies from patients lost to follow-up or because they are retrospective, consistent data suggest that unrecognized toxicity causes a significant burden and is an important unmet need for large numbers of patients. What does seem clear is that of all the symptoms that can arise after pelvic radiotherapy, bowel symptoms frequently have the greatest effect on the quality of life [103].

Clinician-rated toxicity scores often rely on a retrospective review of case notes. This assumes that no toxicity report equates to no toxicity rather than that the right questions may not have been asked [194]. A recent retrospective study [195] comparing patient and clinician reports of acute GI toxicity during chemoradiation found significant discrepancies.

There needs to be a better routine measurement of toxicity in clinical practice. Many authorities have highlighted the inadequacies of the Radiation Therapy Oncology Group score, Late Effects Normal Tissue-Subjective, Objective, Management scales and Common Terminology Criteria for Adverse Events. Not only are these insensitive measures of the patient experience, they frequently underestimate the amount of toxicity suffered, but they also do not accurately predict clinical outcomes [196, 197].

It is important to note that patients are also often reluctant to disclose symptoms, either because of embarrassment, not wanting to appear ungrateful about the treatment they have been given [198], thinking that symptoms are inevitable consequences so nothing can be done about them [199], or

wanting to use the time available to discuss issues specifically related to their cancer [178]. One solution is the routine use of patient-reported outcomes that more fully assess the impact of the illness and treatment on physical, psychological, and social functioning [200, 201]. However, without a holistic approach and thoughtful management strategies, progress that will improve quality of life may not be made [146].

SUMMARY AND RATIONAL

Most patients with pelvic RT as a cancer treatment experience some GI and GU toxicities [183, 188]. All patients must have access to well-coordinated, high-quality, multidisciplinary care. If symptoms are anticipated, identified, and correctly managed, patients' QoL may be significantly improved. This work aims to investigate the feasibility of using a mobile application for reporting acute GI and GU toxicities and outcomes reported in patients exposed to pelvic RT (those with genitourinary, gastrointestinal, and gynecological cancers) and correlating CROs and PROs through validated questionnaires. This study intended to provide robust data to support changes to intra-treatment assessment tools and improve patient experience and QoL.

OBJECTIVES AND HYPOTHESIS:

Primary Objectives:

1) Among a cohort of patients receiving pelvic radiotherapy for curative intent, we aimed to evaluate the feasibility of collecting PROs for GI and GU toxicities prospectively and in real-time in a busy tertiary care cancer centre using a mobile application. **Hypothesis**: We hypothesized that prospectively collecting PROs and CROs for GI and GU toxicities in our setting using a mobile application is feasible.
2) Assess the association between PROs and CROs over time to evaluate whether CROs are a good predictor of PROs. **Hypothesis**: Our underlying hypothesis was that there would be

substantial variation in the PROs that the CROs would not capture and that statistically significant discrepancies between PROs and CROs would be detected such that CROs alone are insufficient in capturing the true impact of GI and GU toxicities on patients' quality of life.

Secondary Objectives:

1) Exploring the influence of baseline characteristics on treatment-related GI and GU symptoms and QoL. **Hypothesis**: We hypothesized that the incidence of GI/GU side effects differs by baseline characteristics and that patient-related factors associated with baseline PROs can be predictive of subsequent scores.
2) Assess whether PROs/CROs scores are associated with subsequent patient healthcare outcomes (changes in medications, emergency room (ER) visits, hospital admissions) to assess the utility of PROs for patient triaging and early intervention. **Hypothesis**: We hypothesized that PROs can be used to assess the incidence and early prevention of specific pelvic radiotherapy-related health outcomes.

PREFACE TO MANUSCRIPT:

There are four areas of importance for all cancers: prevention, early diagnosis, optimizing therapy, and living with and beyond. Despite the increasing number of long-term survivors, little has been done to ensure early assessment and treatment of side effects of cancer therapies, mainly when radiotherapy has been administered. Many patients' symptoms become part of everyday life, 'normality' is adjusted, and these changes are tolerated even if severely limiting activities [146].

Radiotherapy research has primarily focused on the improved delivery of combinations of treatments that have achieved better survival but not necessarily improved the burden of significant toxicities, which are substantially more frequent than commonly acknowledged [202, 203].

Quality of life is a complex tool, going far beyond the regular medical evaluation of treatment toxicity. A comprehensive QOL assessment requires considering several physical, social and psychological factors [204, 205]. PROS are reports patients provide about their health, quality of life, or functional status related to the health care or treatment they have received. Including PROs with clinical outcomes in research and clinical practice provides a more complete understanding of the impact of an intervention, therapy, and/or service on the patient and supports the development and evaluation of healthcare service delivery and quality improvement.

We expected that our findings would reveal an advantage to incorporating PROs during treatment by improving communication between patients and physicians, enhancing patient management, improving their quality of life, and helping to detect adverse events at earlier time points.

This manuscript will be submitted to the Radiation Oncology Journal and has been drafted following its guidelines.

MANUSCRIPT:

Evaluation of Gastrointestinal and Genitourinary Side Effects of Pelvic Radiotherapy: Association Between Patient-Reported Outcomes and Clinician-Reported Outcomes

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Abbreviations:

- Common Terminology Criteria for Adverse events (CTCAE)
- Clinicians reported outcomes (CROs)
- Emergency room (ER)
- European Organisation for Research and Treatment in Cancer (EORTC)
- Food and Drug Administration (FDA)
- Gastrointestinal (GI)
- Genitourinary (GU)
- Patient Reported Outcomes (PROs)
- Quality of life (QoL)
- Radiotherapy (RT)

ABSTRACT

Objectives: This study aimed to investigate the feasibility of collecting electronic patient-reported outcomes (ePROs) for gastrointestinal (GI) and genitourinary (GU) toxicities prospectively and in real-time in a busy tertiary care cancer centre, using a mobile application, assess the association between PROs and clinician-reported outcomes (CROs) over time, exploring the influence of baseline characteristics on treatment-related GI and GU symptoms and quality of life (QoL) and whether PROs/CROs scores are associated with subsequent patient healthcare outcomes.

Patients and Methods: This study used data collected from participants receiving curative pelvic radiotherapy between July 2022 and July 2023. Participants completed validated electronic PROs questionnaires on acute GI/GU toxicities and QoL via a mobile application (Opal). These questionnaires were administered at baseline after each intra-treatment (ITT) visit and at 2- and 12-week follow-up visits. The treating physician filled in the traditional ITT forms simultaneously.

Results: A total of 102 patients were included. 85% of patients responded to ≥80% of the questionnaires, with 91% average adherence to completion. Patients reported more adverse events than assessed from CROs ($p < 0.001$ for most common adverse events). Although Somer's D test demonstrated an association between patient and physician score groups, concordance between PROs and CROs on an individual patient basis was generally poor, e.g., weighted kappa 0.24 for diarrhea.

Conclusion*:* Recruitment for ePROs during radiotherapy was feasible, and adherence to self-reporting was high. Patients reported more adverse events than CROs; therefore, adverse events might be underestimated if PROs were not used.

Key Words: Gastrointestinal, Genitourinary, Side Effects, Pelvic Radiotherapy, Patient-Reported Outcomes, Clinician-Reported Outcomes.

INTRODUCTION

Symptoms may go unnoticed for patients with cancer treated with radiotherapy, as digital monitoring of patient symptoms is not integral to radiation oncology. Many patients are affected by this as radiotherapy contributes to the cure or palliative care of >50% of patients diagnosed with cancer [206, 207]. Even though modern radiotherapy techniques and technologies have reduced the severity of treatment-related toxicity, adverse events (AEs) still substantially impact patients' everyday lives [207]. They receive their treatment in an outpatient setting with limited time for the clinicians to assess the severity of their acute symptoms and initiate supportive care. Evidence shows that chemotherapy-related symptoms tend to be under-reported by clinicians compared to patient reporting [208, 209]. Having patients report their symptoms during treatment has made it possible to detect symptoms earlier and intervene earlier during chemotherapy [210]. Improved outcomes have been established when real-time symptom monitoring is used among patients with cancer in systemic treatment [211-214]. Real-time tracking of PRO allows for timely patient-centred care [211, 213].

Adverse events have been variously assessed in radiotherapy using clinician-reported outcomes (CROs) and patient-reported outcome measures (PROs) [215, 216]. The optimal adverse events data collection method is unclear, and no gold standard exists. The methodology of each assessment type differs, and the scales used for scoring the different assessments vary. Unlike chemotherapy, the recording of radiotherapy toxicity is still inconsistent [192, 217]. Studies with patients in radiotherapy found that patients reported symptoms earlier and more frequently than physicians. A higher rate of patients reporting clinically meaningful symptoms was found than clinicians reporting [218, 219].

Patient-Reported Outcomes (PROs) engage patients in directly providing measures of their health status without clinician interpretation [220]. PROs give the patients' perceptions of their cancer's impact and treatment effects [221] within the framework of the question asked. Clinicians monitoring and using PROs responses may improve patient-clinician communication and patient satisfaction and enhance symptom recognition and assessment [211, 222].

In addition to being used in clinical care, PROs are recommended in comparative effectiveness research [44]. A clinical benefit of novel technical innovations in radiation oncology is expected; however, systematic prospective evaluation of clinical effectiveness is scarce [223]. PROs data completes the picture by enabling the provider with real-world evidence of treatment safety directly from the patients [224].

A key challenge when electronic PROs (ePROs) are incorporated into cancer treatment is that implementation process considerations are often not addressed [222]. Previous studies found that using mobile apps for symptom reporting during pelvic radiotherapy has been reported as acceptable by patients [225, 226]. However, the purpose of incorporating PRO in the specific clinical setting for a particular patient group must be considered carefully. To reduce the risk of PROs not bringing meaningful change to the patient, the feasibility of self-reporting must be explored for direct insight into the perceived value for the patients in the specific setting [222, 227, 228]. A few studies have investigated PROs in radiotherapy for symptom management [229, 230] and the feasibility of incorporating ePROs during radiotherapy [225, 231, 232]. In one of the studies, patients without an email address were excluded [225]. Two other studies offered patients an alternative option to web-based reporting at home [232]: an automated telephone system or patients being approached with a computer in the clinic waiting area [231]. Therefore,

there is a need to investigate integrating ePROs into the clinical workflow of radiotherapy with a simple setup being feasible for all patients.

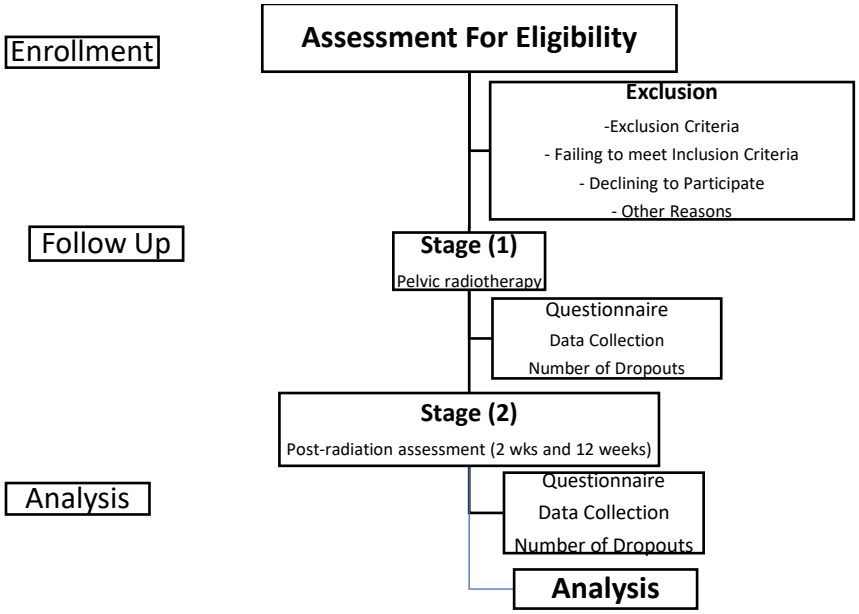
This study examined the feasibility of using ePROs among patients with pelvic cancer treated with radiotherapy of a curative intent to ensure sustainability in integrating ePROs in radiation oncology. It also explored the degree of concordance on an individual patient level between PROs and CROs. In addition to the influence of baseline characteristics on reported toxicities and whether PROs are associated with specific health outcomes, e.g., change in medication or ER visits. The overall aim was to assess the capability of using PROs as adverse events assessment tools in clinical radiotherapy settings.

METHODS

Study Design

The proposed research was a prospective study in a cohort of 102 patients undergoing radiotherapy for pelvic tumours. The flow chart in figure (1) and supplementary table (1) demonstrates an overview of the study procedure.

Figure (1): Flow chart of the planned study



Setting

This single-centre trial was conducted at McGill University Health Centre (MUHC), Montreal, Quebec, Canada.

Participants

All patients receiving RT to the pelvis for curative intent at the McGill University Health Centre (MUHC) Radiation Oncology clinic were eligible.

Inclusion and Exclusion Criteria: We had established a set of inclusion/exclusion criteria for participants (table 1).

Table (1): Inclusion and exclusion criteria

Inclusion criteria	Age: 18 years or older
	Pelvic malignancy
	No previous pelvic radiotherapy
	ECOG performance status of 0–2
	Able to provide informed consent
	Capable of reading and understanding English or French
Exclusion criteria	Patients who have received prior pelvic radiation
	Patients at the end-of-life (expected survival less than 6 months)
	Patients suffering from inflammatory bowel disease (IBD) or collagen vascular diseases (CVD).
	Patients included in other QoL studies may increase the patient burden and bias in answering questionnaires.

Of note, patients receiving concurrent or prior chemotherapy and patients who have undergone any previous surgery, including lower anterior resection and abdominoperineal resection, were permitted.

Recruitment:

Radiation oncologists identified eligible participants at their first outpatient clinic appointment. After an introduction from the radiation oncologist, a research team member approached interested patients, gave them a detailed explanation of the study, and offered the informed consent form (ICF) to those interested. Patients could take the ICF home, and a research team member called

within 24-48 hours to answer all the patient questions. The research team assessed the eligibility of patients willing to participate, obtained written informed consent, gave the patients instructions on the use of the mobile application, and invited them to fill out the baseline questionnaire. At all recruitment time points, the research team recorded reasons for non-participation. Patients were informed at the point of consent that they could withdraw at any time. No reason was required. The planned completion was 12 weeks after enrollment of the last patient.

Demographic and Clinical Datapoints

We extracted from the database information on patient demographics and clinical information such as age, gender, comorbidities such as diabetes, hypertension, hyperlipidemia, pre-existing GI disease, pre-existing GU disease, autoimmune disorders, current medications, smoking status, and treatment-specific information such as prior chemotherapeutic agents, radiation dose and fractionation.

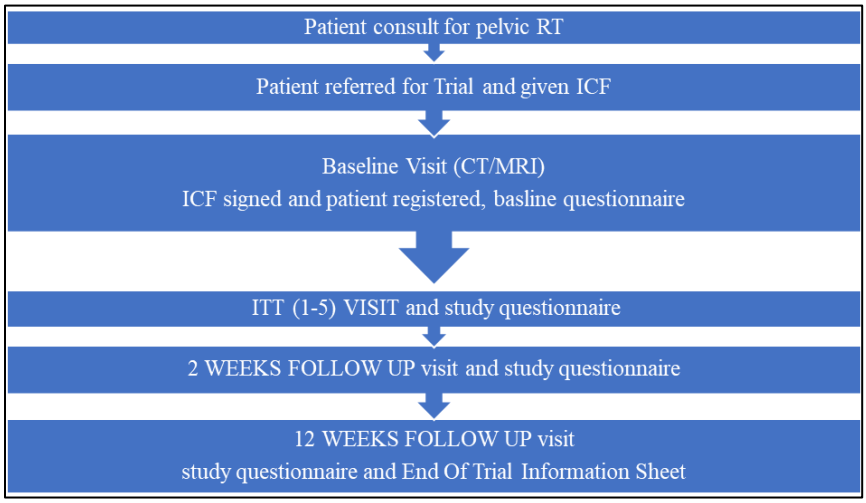
Study Procedures:

The standard treatment duration for patients receiving standard or hypo-fractionated (radiotherapy is given over a shorter period of time than standard radiation therapy [233]). RT for curative intent to a pelvic malignancy is three to five weeks. Enrolled Patients completed GI/GU and QoL questionnaires using the mobile application (Opal) at baseline, within 24 hours after each intra-treatment (ITT) visit, and at two subsequent time points, i.e., at 2-and 12-week follow-up visits after completion of treatment (figure 2). In addition, participants answered three questions about whether they visited the ER, were hospitalized, and/or had any medication changes over the last week. A trained research assistant entered questionnaire data into the database. All data were kept in a password-protected database and under hospital firewall protection and were anonymized by coding for analysis. The treating physician assessed side effects using the conventional ITT form

(Supplementary Table (2)) that documents symptoms including diarrhea, proctitis, bladder spasm, dysuria and urinary frequency. These toxicities were graded using common terminology for clinical adverse events (CTCAE version 5.0) [234], and management decisions were made accordingly to address symptoms when applicable. The investigator described and reported all adverse events (AEs) or serious AEs (SAEs) obtained from the patient medical record. Only patients with at least two or more available PROs and corresponding CROs symptom assessments were included in the analysis.

***Blinding*:** The treating physician and the radiation oncologist were blinded to consent for study participation and remained blinded in all visits during treatment. We chose to administer the questionnaires and arranged for a follow-up visit with the clinician 2 weeks after treatment because we wanted to capture the remaining acute symptoms reported by the patient after treatment, which usually resolves within three weeks after radiotherapy [158]. As this is not part of routine care, the clinician would likely be aware of the study participation, and this is considered one of the study limitations as the blinding process was not effectively implemented and potentially influenced the study outcomes.

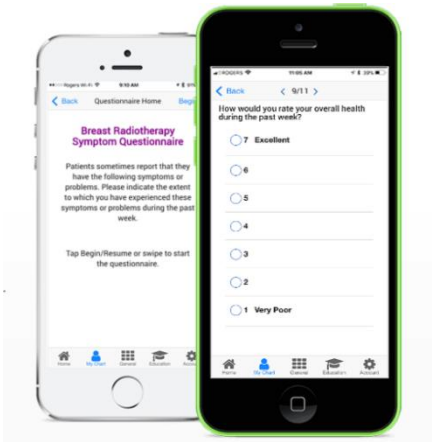
Figure (2): Patients Flow through the trial.



Opal Mobile Application

Opal is a *patient portal* for patients at hospitals in Quebec designed to empower patients with their medical information (figure 3). It is a smartphone app for patients and a live dashboard for clinicians currently used at the MUHC. It gives registered patients access to contextualized medical data and personalized educational material, including appointments, lab results and medical notes, a virtual waiting room, and symptom questionnaires, and allows them to check-in and be notified for appointments using their smartphones [235].

Figure (3): Opal application interface



Questionnaires

Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE™)

The US National Cancer Institute (NCI) developed and validated the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) for quantifying symptomatic adverse events in cancer clinical trials. It was designed to enhance the validity, reliability, and precision with which symptomatic adverse effects of treatment were assessed in patients in cancer clinical trials [64, 236, 237]. The PRO-CTCAE item library comprises items that capture the full range of symptomatic treatment effects experienced across various disease

sites and cancer treatment modalities, and it has been linguistically validated in English and French [238].

In our study, pelvic radiotherapy-associated GI/GU toxicity data was collected prospectively via the **PRO-CTCAE™** electronic questionnaire. The choice of PRO-CTCAE module items depended upon this study's aims, and we used the Form Builder to build a study-specific custom form (supplementary table (3)). GI items included nausea, vomiting, flatulence, bloating of the abdomen, constipation, diarrhea, abdominal pain, and loss of control of bowel movements. Urinary symptoms include the urge to urinate suddenly, frequency, urine colour change, loss of urine control (leakage) and painful urination (dysuria).

Patients self-reported the frequency of each symptom on a scale from 0 to 4 (or 0 for "none," 1 for "mild," 2 for "occasionally," 3 for "frequently," and 4 for "almost constantly"). For some symptoms, the patient reported on a severity scale ranging from 0-4 (0/1 for "mild," 2 for "moderate," 3 for "severe," and 4 for "very severe").

The European Organisation for Research and Treatment in Cancer QLQ-C30 (EORTC QLQ-C30) Questionnaire

The EORTC QLQC30 is one of the most widely used questionnaires in oncology for assessing Health-Related Quality of Life (QOL). The questionnaire is available in more than 110 different languages. The reliability and validity of the QLQ-C30 are highly consistent across different language and cultural groups [71, 83]. The QLQ-C30 consists of 30 items grouped into 15 domains covering symptoms commonly reported in oncology, such as pain and fatigue, as well as areas of functioning essential to cancer patients, such as physical function, social function, and global-health status scale (GHS). For the functioning scales and GHS, higher scores represent a

higher degree of functioning, while the higher the score for symptom scales, the higher the level of symptom burden [239].

In our study, patients self-reported QOL in real-time electronic PROs questionnaires (EORTC QLQ CX24, EN 24, C30). We chose Questions 29 and 30 (Supplementary Table (4)) to ask the patients to rate their overall health and QOL during the past week on a scale between 1-7, where one is equivalent to "very poor" and seven is "excellent." Responses to these two questions were combined during scoring into a single global quality of life scale ranging from 0 to 100 with higher scores indicating better quality of life.

Health Outcomes Assessment Questionnaire (HOAQ):

In addition, participants were asked to answer three yes or no questions about if they had ER visits, hospitalization, and medication changes (Supplementary Table (5)).

OUTCOME MEASURES

Baseline Data:

We collected:

- Baseline demographic and clinical data (age, diagnosis, chemotherapy, and RT treatment parameters)
- Physical parameters, including height, weight, and gender
- Confirmation of eligibility
- Verification of written informed consent
- Internet access
- Comorbidities (diabetes, hypertension, hyperlipidemia, smoking status, pre-existing GI disease and pre-existing GU disease)
- ECOG performance status
- Smoking status

Primary Outcome Measures:

The primary objective of this study was to evaluate the feasibility of collecting PROs and CROs for GI and GU toxicities prospectively and in real-time in a busy tertiary care cancer centre. The questionnaire completion rate was calculated as the number of questionnaires with at least five questions answered divided by the total number of potential questionnaires that could be administered through the study. The attrition rate was defined as the number of patients who signed the consent form but did not complete the questionnaires as a proportion of the total number recruited. The reasons for non-compliance were documented.

The second primary outcome measure for assessing the association between PROs and CROs and for assessing predictors of PROs was the PRO-CTCAE symptom scores and the global QoL score from the EORTC QLQ-C30 evaluated using self-reported patient data collected on electronic questionnaires.

The PRO-CTCAE questionnaires items included patient adaptations of CTCAE symptom items salient to individuals receiving pelvic radiotherapy (listed in table 2). Each PRO-CTCAE symptom was considered as a separate outcome and correlated with its corresponding CTCAE Version 5.0 Term:

Table (2): PRO-CTCAE Symptom Term Corresponding CTCAE Version 5.0 Term

PRO-CTCAE Symptom Term	Corresponding CTCAE Version 5.0
Vomiting	Vomiting
Gas	Flatulence
Bloating	Bloating
Diarrhea	Diarrhea
Abdominal pain	Abdominal pain
Fecal incontinence	Fecal incontinence
Painful urination	Urinary tract pain
Urinary urgency	Urinary urgency

PRO-CTCAE Symptom Term	Corresponding CTCAE Version 5.0
Urinary frequency	Urinary frequency
Change in usual urine colour	Urine discoloration
Urinary incontinence	Urinary incontinence

Secondary Outcome Measures:

As a secondary outcome, we measured the influence of baseline characteristics such as age, gender, comorbidities (such as diabetes, hypertension, hyperlipidemia, pre-existing GI disease and pre-existing GU disease), smoking status, and treatment-specific information such as prior chemotherapeutic agents, radiation dose and fractionation on treatment-related toxicity or QoL. These were assessed by correlating the characteristics with the PRO-CTCAE symptom scores and the global QoL score from the EORTC C30.

In addition to assessing the usability of PROs to triage patient symptoms by correlating PROs/CROs evolution of scores with clinical management, changes were assessed by patient-reported clinical information such as changes in medications, ER visits, and hospital admissions and correlating these outcomes with the given scores.

STATISTICAL CONSIDERATION

Sample Size and Power Calculation:

Although, formal power calculations are not necessary for achieving our first primary objective (feasibility of the intervention) [240, 241], we calculated the sample size that would be needed to achieve adequate statistical power for our second primary objective. In order to minimise the sample size, we calculated the sample size with ordinal logistic regression with diarrhea PRO-CTCAE scores as the outcome, using the method by Whitehead [242] . Due to the repeated measures design of our study, we also used a variance inflation factor to adjust the target sample size for intra-subject correlation [243]. This method assumes independence of observations;

independence such that measurements for each sample subject at each timepoint are not related to the measurements of other subjects or other timepoint measurements.

The reason we based our sample size calculation on prevalence of radiotherapy related diarrhea is that diarrhea is the most common adverse event of pelvic radiotherapy; approximately 30–50% of patients have been reported to experience pelvic radiation-induced diarrhea [244], with a higher incidence observed in patients treated with concurrent chemotherapy [245]. We assumed that PRO-CTCAE baseline scores would be distributed similarly to Sedhom [246], who found that at baseline, 33% of cancer patients had a PRO-CTCAE score of >0 and 5% had a score of ≥3 for frequency of diarrhea; our assumed prevalence of grade 0-4 scores at baseline was therefore 0.67, 0.19, 0.09, 0.03, and 0.02. Tom suggests that the prevalence of clinician diarrhea CTCAE grade >0 at baseline is likely to vary between 10-50% [15]; therefore, we assumed a conservative exposure prevalence of 20% for the sample size calculation. We assumed that PRO-CTCAE scores and clinician CTCAE scores would be associated with an odds ratio of at least two based on Behroozian [247]. We expect a 30–35% attrition over three months, as per the literature [34]. We, therefore, expected an average of 5 measurements per participant if 35% of the eight measurements per patient were missing. We assumed an intraclass correlation coefficient of 0.1 for the variance inflation. All calculations were for a two-sided alpha of 0.05.

Based on the above assumptions, 521 independent observations would be required to achieve a power of 90% to detect an odds ratio of 2. This corresponds to 105 participants, assuming an average of 5 observations per participant after accounting for attrition. Adjusting the sample size with the variance inflation factor led to a final target sample size of 147.

Statistical Analyses:

Descriptive analyses

Patient and treatment demographics were summarized using frequency distributions for categorical variables and means (standard deviation, SD), medians (inter-quartiles), and ranges for continuous variables. We presented the cross-tabulation of CTCAE grades by matching PRO-CTCAE scores for all time points combined. The distribution of PRO-CTCAE scores, QoL scores, and CTCAE grades was also presented separately for each time point using summary statistics and graphical representation.

Primary Objective 1: feasibility of collecting PROs and CROs for GI and GU toxicities.

The proportion of missing data for each item and questionnaire completion at each time point were summarized. We assessed whether there were systematic differences in demographic and clinical characteristics between patients with missing and non-missing data using the chi-squared and Wilcoxon rank-sum tests for categorical and continuous variables, respectively.

The practicality of the recruitment approach was assessed by summarising the screening, eligibility, and consent processes, including the number of patients participating at each stage.

Primary Objective 2: Assess the association between PRO and CROs over time

PRO-CTCAE is an item library designed for eliciting patient-reported adverse events in oncology. For each adverse event, up to three individual items are scored for frequency, severity, and interference with daily activities. To align PRO-CTCAE with other standardized tools for adverse event assessment including CTCAE, we used a validated algorithm for mapping individual items for any given adverse event to a single composite numerical grade. Final scoring algorithm for mapping of PRO-CTCAE individual item score combinations to single composite adverse event grade are shown for all PRO-CTCAE combinations, including those with three items, two items,

and one item. In this validation study, composite grades performed well and comparably to individual item scores on validity, reliability, sensitivity, and between-arm delineation [248]. Table 3 shows composite grading for one item.

Table (3): One item PRO-CTCAE corresponding composite grades

FREQUENCY	**COMPOSITE GRADE**
Never	0
Rarely	1
Occasionally	1
Frequently	2
Almost Constantly	3
SEVERITY	**COMPOSITE GRADE**
None	0
Mild	1
Moderate	2
Severe	3
Very Severe	3
AMOUNT	**COMPOSITE GRADE**
Not at all	0
A little bit	1
Somewhat	1
Quite a bit	2
Very Much	2

We assessed the association between corresponding PROs and CROs over time using Somers' D statistic, weighted kappa statistic, Mcnemar Bowker's symmetry test and multilevel random effects regression models (a measure of correlation controlling for covariates).

Somers' D statistic is a nonparametric measure of the strength and direction of association between an ordinal dependent variable (PRO-CTCAE scores) and an ordinal independent variable (clinician CTCAE score). Somers' D takes values between -1 and 1; values close to 0 indicate a poor predictive ability of the independent variable, while values close to 1 indicate a strong positive correlation, and values close to -1 indicate a strong negative correlation.

The kappa statistic measures the agreement of two ordinal subjects with identical categories. Guidelines for interpreting the value of weighted kappa in terms of the strength of agreement

were <0.20: poor; 0.21–0.40: fair; 0.41–0.6: moderate; 0.61–0.8: good; 0.81–1.00: very good [249].

Mcnemar Bowker's symmetry test examined whether patient-reported and corresponding clinician-reported CTCAE scores were symmetrically distributed. A significant p-value suggests that responses from patients and clinicians were not symmetric (for example, if patients were more likely to respond '1' on PRO-CTCAE when their clinician gave a '0' CTCAE score than to respond '0' on PRO-CTCAE when their clinician gives a '1' CTCAE score) [250].

The multilevel models included a random intercept per participant to account for repeated measurements on the same participant.

Different models were fit to each PRO:

- For PRO-CTCAE items on the 0-3 scale, we used ordinal logistic regressions; an ordinal logistic regression is a variation of the logistic regression for ordinal data which assesses the odds of being in a higher-level category across all levels of the scale simultaneously and pools the results across all levels (odds of 0 vs 1-3, 0-1 vs 2-3 and, 0-2 vs 3). Ordinal logistic regressions do not require the dichotomization of an ordinal categorical outcome but require a proportional odds assumption. If the proportional odds assumption was not met across category levels, we used binary logistic regression instead, with the outcomes dichotomized as a symptom score of 3 vs. <3. A symptom score of 3 on the PRO-CTCAE indicates that a symptom was expressed "Almost constantly" (>3 times/day).
- We used binary logistic regressions for PRO-CTCAE items on the yes/no scale.
- For QoL scores, we used a beta regression. A beta regression was used when the outcome was a percentage or proportion between 0-1. It was the most appropriate option in this case because

the QoL scores were a continuous value bounded between 0-100; the scores were transformed to a percentage value between 0-1 for the regression.

Model predictors included the clinician reported CTCAE, time since the study baseline and patient demographic and clinical characteristics. The inclusion of the clinician CTCAE score as a categorical predictor assessed if higher clinician CTCAE scores were associated with higher patient symptom scores and lower quality of life. The inclusion of time as a categorical predictor accounted for changes in PROs over time since the start of treatment. The inclusion of patient characteristics controlled for confounding by demographic and clinical features.

Secondary Objective 1: exploring the influence of baseline characteristics on treatment-related GI and GU symptoms and QoL.

We assessed the association between PROs and baseline patient characteristics over time using multilevel random effects regression models. The same regression models used above for the first secondary objective were refitted with time and baseline characteristics only as predictors (clinician CTCAE scores were removed as a predictor from the models).

Secondary Objective 2: Assess whether PROs/CROs scores were associated with changes in medications, ER visits, and/or hospital admissions

We assessed the association between PROs and other patient outcomes over time using multilevel random effects logistic regression models. The models included a random interpretation per participant to account for repeated measurements on the same participant. The modelled outcomes were whether the patient experienced a change in their medication, an ER visit, or a hospital admission during the week study before each visit. Separate models were fit for each outcome (changes in medication, ER visits, hospital admissions). The patient PRO-CTCAE score measured at the visit at the start of each interval was included in the model as the main exposure of interest

to see if the PRO-CTCAE is associated prospectively with each outcome during the subsequent interval. Time was included as a categorical predictor in the model to account for changes in the risk of these outcomes by time since the start of treatment. Interactions between time and PRO-CTCAE scores were assessed to explore whether there were certain weeks were patient PRO-CTCAE scores were more predictive of outcomes. Patient demographic and clinical characteristics and clinician CTCAE score were included as predictors to control for confounding and to assess the independent predictive value of the patient PRO-CTCAE score.

All analyses were conducted using IBM SPSS Statistics version 29.0.0.0 (241). A p-value <0.05 was statistically significant.

RESULTS

A total of 102 patients who underwent a course of pelvic radiotherapy from July 2022 to July 2023 were included in the study. All participants completed at least one intra-treatment, and one follow-up questionnaire. Baseline patient and treatment characteristics are summarized in Table (4).

Table (4): Baseline characteristics of the study participants.

Total Number of Patients	**N = 102**	
Age	Median 68 (Range 43 - 85)	
Gender	N	%
Female	17	16.7
Male	85	83.3
BMI		
Less Than 18.5	2	1.0
18.5 - 24.9 (Average weight)	22	14.6
25 - 29.9 (overweight)	50	37.5
30 or More (obese)	28	24.0
ECOG Performance Status		
ECOG 0	91	89.2
ECOG 1	10	9.8
ECOG 2	1	1.0
Co-Morbidities		
Diabetes	17	16.7

Hypertension	35	34.3
Dyslipidemia	36	35.3
Pre-Existing GI Disease	8	7.8
Pre-Existing GU Disease	9	8.8
Smoking Status		
Non-Smoker	85	83.3
Smoker	3	2.9
Ex-Smoker	14	13.7
Cancer Diagnosis		
Anorectal Carcinoma	21	20
Endometrial Carcinoma	11	10.8
Cancer Prostate	64	62.7
Cancer Bladder	6	5.9
Adjuvant Therapy		
None	30	29.4
Chemotherapy	36	35.3
Hormonotherapy	36	35.3
Mode of Fractionation		
Normal Fractionation	18	17.6
Hypo-Fractionation	84	82.4

Most patients informed about the study consented to participate (consent rate 69 %). Those who declined were mostly older patients (median age of 74). The reason cited for declining was, most often, not being able to report electronically, although 84.4 % of those who declined participation had no device for reporting. Seven patients were withdrawn by the physician due to ineligibility for radiation or contraindication discovered after consenting; two failed to register in Opal due to technical issues; eight patients left the study before starting treatment; two dropped out after treatment, and one died after the first follow-up (attrition rate 15.7%). Reasons for non-participation retention during follow-up, including the number of patients withdrawing from the study, the timing and reasons for withdrawal are presented in figure (4).

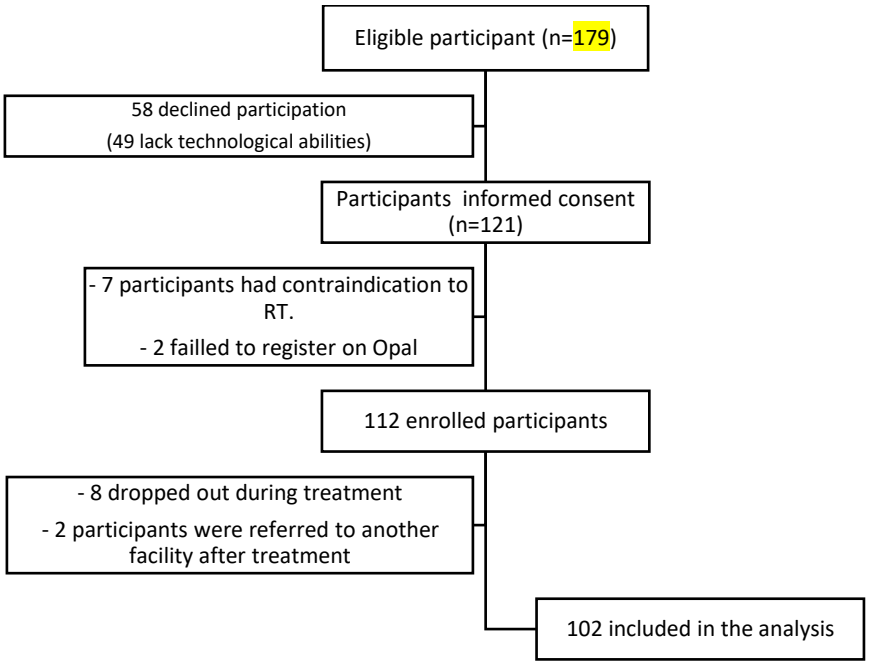


Figure (4): Flow chart of the study.

Overall, 1383 of the 1521 questionnaires distributed at 3–7 time points were completed (average completion rate 90.9%). Reasons for missing responses were not collected systematically; however, participants often relayed to the research assistant that they sometimes encountered server errors, and then they either forgot or were too tired to return to it.

Before treatment, around 91.6 % of the patients filled out the baseline questionnaires. The average patient adherence to completion during treatment was 91.4 %, and the average adherence to follow-up weeks 2 and 12 was 88.9 % for participants enrolled in the study at both timepoints. 90% of the participants received additional reminders or text messages to remember to respond when they haven't done so. Overall, PROs completion rates were very high; throughout the study period, there was no statistically significant change in the PROs' completion rates over time. Table (5) shows the completion rate for the three study questionnaires.

Table (5): PROs completion rate (N/%).

	Uncompleted	Partially Completed	Completed
The NCI PRO-CTCAE Questionnaire, N = 507	29 (5.7%)	25 (5.0%)	453 (89.3%)
The EORTC QLQ-C30 Questionnaire, N = 507	30 (5.9%)	13 (2.6%)	464 (91.5%)
The *HOAQ*, N = 507	32 (6.3%)	9 (1.8%)	466 (91.9%)
TOTAL / N=1521	91 (6.0%)	47 (3.1 %)	1383 (90.9%)

Figure (5) represents the number of participants fully completed the three questionnaires per visit the mean participants' completion rates over time.

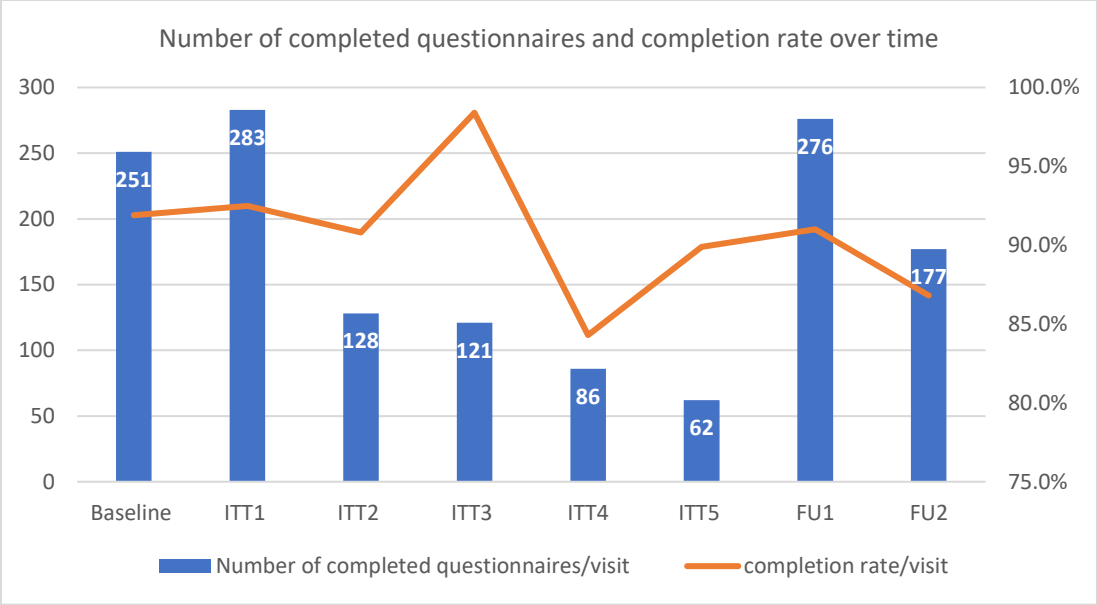


Figure (5): Mean PROs completion rate over time.
ITT = intra-treatment visit, FU1=2 weeks follow-up visit, FU2=12-week follow-up visit.

Average Completion rate of scheduled CROs was 81.7 % of intra-treatment visits during treatment, 78.2 and 61 % for 2 and 12 weeks of follow-up, respectively. Figure 6 shows the average completion rate for physician documentation of toxicities over time.

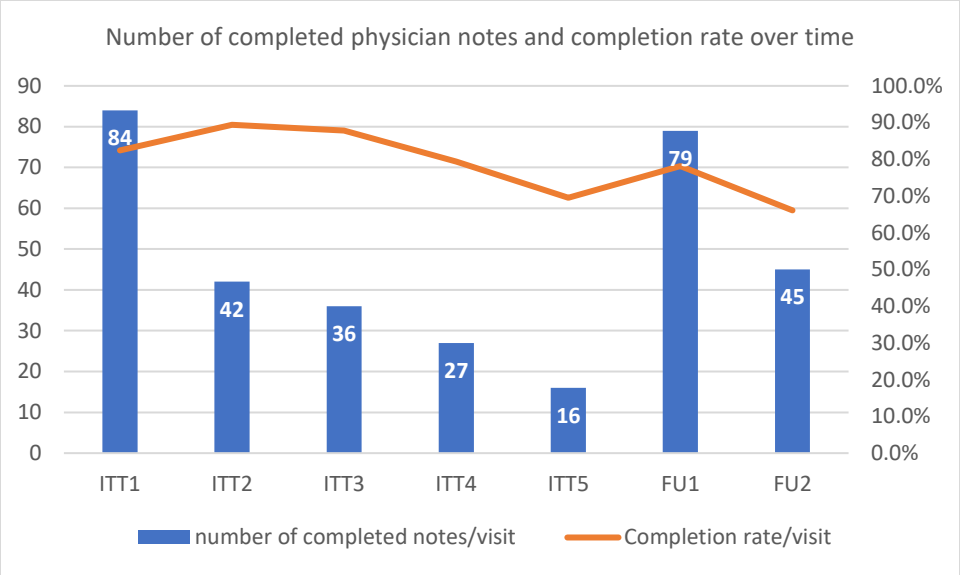


Figure (6): Physician notes completion rate over time.

ITT = intra-treatment visit**,** FU1=2 weeks follow-up visit**,** FU2=12-week follow-up visit.

According to collected CROs, frequency and diarrhea were reported the most, 20 % and 17%, respectively, followed by dysuria (8%) and proctitis (6%). All toxicities reached a maximum during therapy. Urinary frequency still manifested in most patients at 2 and 12 weeks of follow-up. Diarrhea, dysuria, and proctitis were better than at baseline but still present in a few patients. Bladder spasms had resolved at the follow-up for all patients. The only statistically significant change in reporting over time was for diarrhea, as reporting diarrhea significantly increased during treatment and resolved after treatment. Figure 7 shows CROs toxicity scores, as indicated in the methods section.

The PROs toxicity profile over time was the same as CROs, with toxicity increasing during therapy. Frequency and urgency measures decrease but remain above baseline at 12 weeks of follow-up. The same tendency with decreasing toxicity but with a higher baseline was seen for dysuria. Diarrhea reached the maximum during treatment and declined to baseline at 12 weeks. Unchanged reporting rates for loss of control of urine (leakage) and abdominal pain, while nausea, vomiting, bloating and loss of control of bowel movements increased slightly at the 2-

week follow-up, then resolved or were below the baseline at 12 weeks follow-up. Figure 8 shows PROs toxicity scores over time. Notably, most PRO scores were much higher than the corresponding CRO scores; for instance, dysuria was reported by patients up to 27 % and frequency in 26.4%, while the corresponding percentage in CROs was 8% and 20%, respectively.

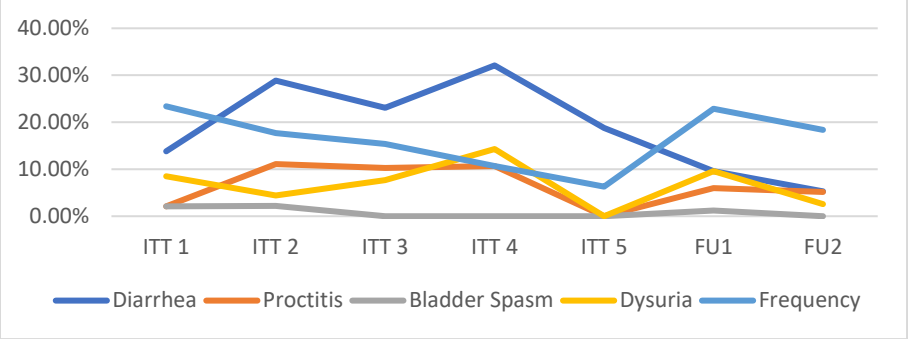


Figure (7): Clinician reported toxicities over time.
ITT = intra-treatment visit, FU1=2 weeks follow-up visit, FU2=12-week follow-up visit.

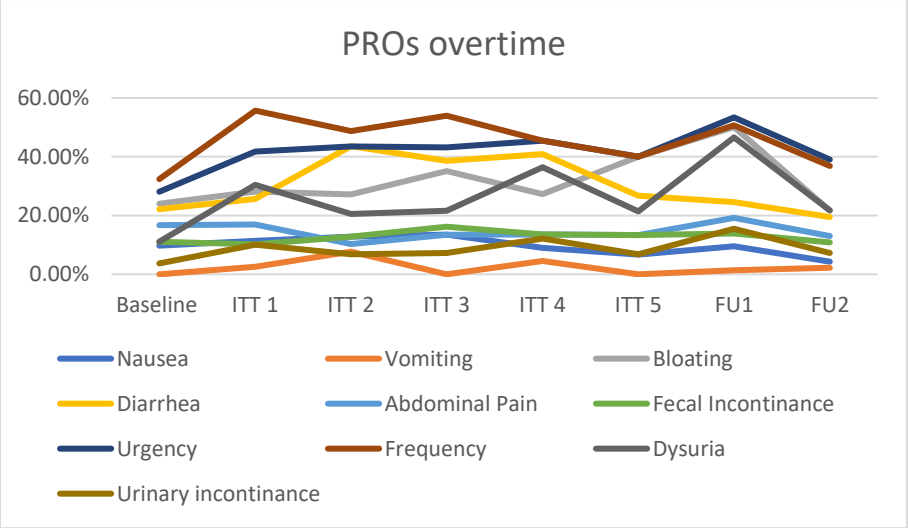


Figure (8): Patient-reported toxicities over time.
ITT = intra-treatment visit, FU1=2 weeks follow-up visit, FU2=12-week follow-up visit.

Participants rated their overall health and QOL during the past week on a scale between 1-7, where one is equivalent to "very poor" and seven is "excellent." Responses to these two questions were combined during scoring into a single global quality of life scale ranging from 0 to 100 with higher scores indicating better quality of life. We used the anchor based method to compare relevant

differences in scores between timepoints and interpreted the results using a previously defined ***clinically meaningful difference*** (the smallest change in an outcome that an individual patient would identify as important and which would indicate a change in the patient's management) whereby ‘a little’ change for better or worse, for score changes from 5 to 10, ‘moderate’ change with score changes from 10 to 20, and ‘very much’ change corresponding to a change greater than 20 [251, 252].

As shown in figure (9), the overall quality of life and health evaluated by both EORTC questionnaires showed almost undetectable change for better or worse on the scale, where approximately 80% report excellent health and quality of life (score 5-7) for the duration of the study. The changes over time were not statistically significant.

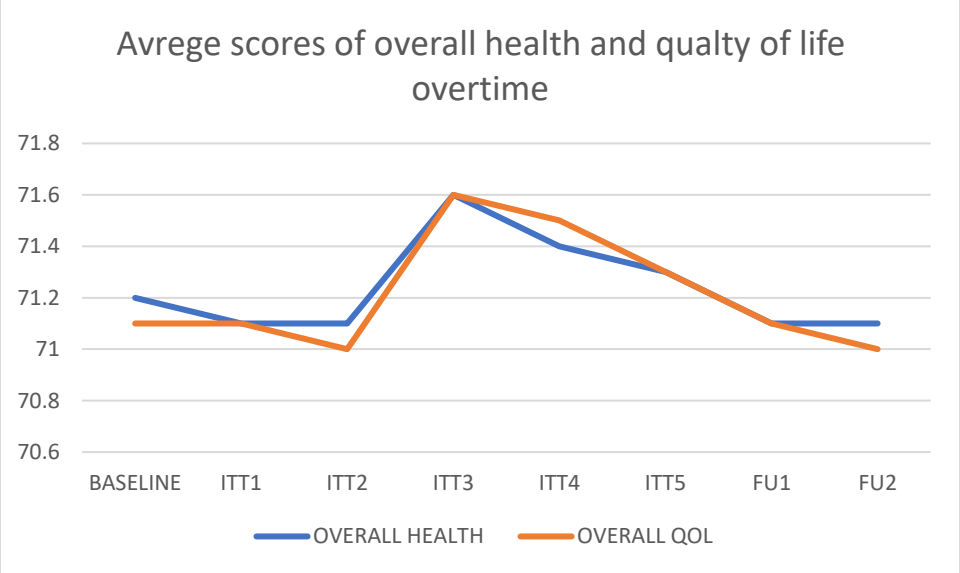


Figure (9): Patient-reported quality of life and overall health status over time.
ITT = intra-treatment visit**,** FU1=2 weeks follow-up visit**,** FU2=12-week follow-up visit.

We paired collected PROs with relative CROs. Clinicians use CTCAE grading to describe toxicities; for most parameters, grade 1-2 toxicity was reported. However, grade 1 was chosen for dysuria (since this reflects the presence of either item or no higher grading is possible). For PROs we used the Composite Grading Algorithm for the National Cancer Institute’s Patient-

Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [248].

We could evaluate the discrepancy with a consistent underreporting in CROs compared to PROs within 927 independent paired observations of patient and physician reports that occurred within three days. Under recognition existed in 375 of 927 (40.5%) observations of patient-reported toxicities, 121 of 309 (39.2%) of patient-reported diarrhea, 177 of 309 (57.3%) of patient-reported bother from frequency, and in 77 of 309 (25%) of patient-reported dysuria. Detailed findings from the concordance analysis between physician and patient reports of selected toxicities (diarrhea, frequency and dysuria) are provided in figure (10) and figure (11).

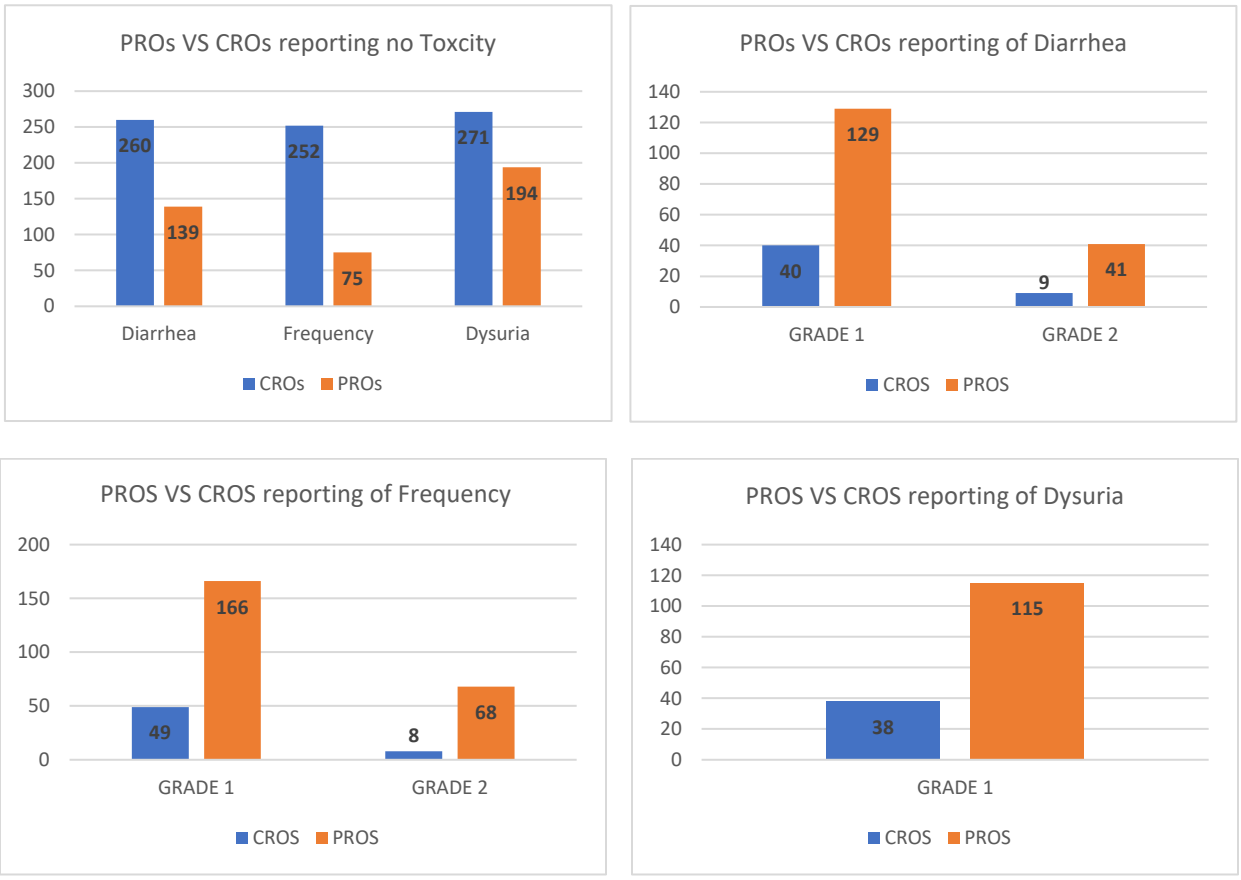


Figure (10): Concordance between physician and patient reports of selected toxicities (diarrhea, frequency and dysuria).

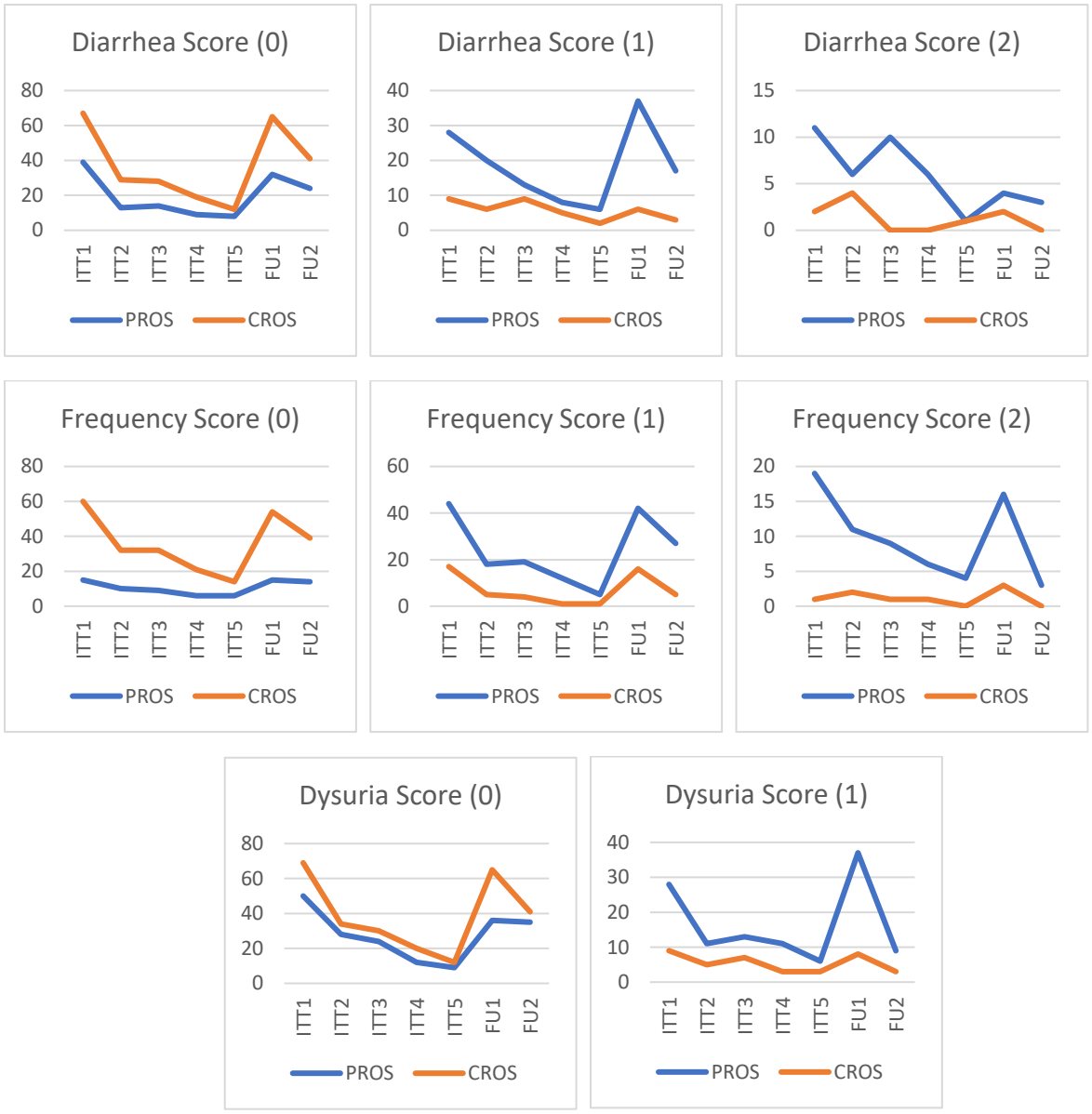


Figure (11): Concordance between physician and patient reports of selected toxicities (diarrhea, frequency and dysuria) over time.

Although Somer's D test demonstrated an association between patient and physician score groups, concordance between PROs and CROs on an individual-patient basis was generally poor (Table 6). Patients reported diarrhea more often than clinicians (figure 10 and figure 11); percentage agreement was 48%, and concordance was poor, as evidenced by the low-weighted kappa (0.24, Table 6). Bowker's test of symmetry was also highly significant ($p < 0.001$),

indicating discordance, with patients reporting side effects more often than clinicians (Table 6). Concerning urinary frequency, patients reported more severe effects than those scored by clinicians (Bowker's test of symmetry <0.001) [Table 6]. The agreement was poor, as was concordance (weighted kappa 0.113) [Table 6]. The same observation was seen for dysuria, with a lower rate of this side effect reported by clinicians (figure 10 and figure 11), and concordance remained poor (weighted kappa 0.187, Table 6). In addition, Bowker's test for symmetry was statistically significant ($p < 0.001$), implying more severe effects reported by PROs than CROs (Table 6). However, as the recommended sample size was based on a single domain "diarrhea", underestimation of results of other domains is possible and future research on a larger sample size accounting for all domains is needed to confirm these results.

Table (6): Concordance between PROs and CROs assessments of specific toxicities.

Statistical testing (Value / Significance)	**Directional Measures**	**Symmetric Measures**	**Chi-Square Tests**
	Somers'd (Ordinal by ordinal)	Kappa (Measure of Agreement)	McNemar-Bowker's Test
Diarrhea	.270 (<.001)	.124(.004)	28.778 (<.001)
Frequency	.214 (<.001)	.113 (.002)	77.751 (<.001)
Dysuria	.236 (<.001)	.187 (<.001)	<.001 (binomial distribution used)

On stratified analysis, to evaluate the associations between baseline characteristics and reported toxicities and quality of life, there was little evidence that reported toxicities varied according to baseline characteristics. Some baseline factors were significantly associated with reported PROs in logistic regression models, but on univariate analysis only and not across all time points. For example, females tended to report dysuria more than males [OR 0.34 (95%CI 0.006–0.201)]. This did not maintain significance in multivariate analysis.

Concerning whether PRO scores were associated with medication changes, ER visits, and hospital admissions, there were not enough events to be able to draw conclusions. Of the 466 health outcomes questionnaires, only 31 participants reported a change in medication (6.7%), 9

participants reported visiting the emergency room (1.9%), and 6 participants reported being hospitalized (1.3%) (figure 12). Most associations found were not statistically significant on Binary Logistic Regression analysis (table 7).

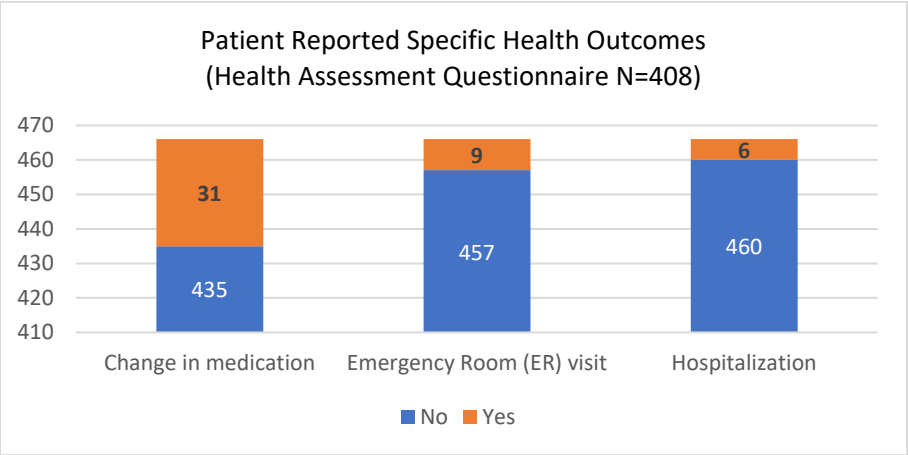


Figure (12): PROs scores association with Specific Health Outcomes

Table (7): Association of PROs scores with Specific Health Outcomes

Reported toxicity	Diarrhea			Frequency			Dysuria		
	Sig.	Exp(B)	95% CI.	Sig.	Exp(B)	95% CI.	Sig.	Exp(B)	95% CI.
Change in Medications	.013	3.035	1.260-7.313	.327	.571	.187-1.749	.165	1.754	.794- 3.879
Hospitalization	.365	2.213	.396-12.359	.793	1.259	.226- 6.997			
Emergency room Visits	.427	2.667	.237-29.959	.515	2.523	.156-	.832	.840	.167- 4.224

However, these results are “non-significant” due to the small sample size. The lack of significance here does not necessarily mean that the chosen domains are not a good predictor of the outcomes; there may be an association but unfortunately, we lack the statistical power to be able to reliably measure the association between the variables.

DISCUSSION

This prospective study investigates PROs reporting via mobile application in patients receiving pelvic radiotherapy for curative intent. The study aimed to explore the feasibility of integrating ePROs and to evaluate the association between PROs and CROs. Also, we investigated the

association between patient demographics and reported symptoms and QoL, as well as the capability of using PROs for patient triage.

The feasibility of collecting e-PROs via Opal

Mobile devices have emerged as an important tool for improving communication between patients and clinicians [253, 254]. Surprisingly, a recent review found only two studies using mobile health apps in oncology, which contrasts with the rapidly growing market of mobile health apps [255]. That may imply that introducing new mobile health tools is much faster than their scientific appraisals [256]. In our study, electronic reporting via the Opal application was feasible and conducted by almost all participants. Our response rate was >90% in eligible patients. The high completion rates indicate that the ePRO reporting using the Opal application was easy for patients to use.

Association Between PROs and CROs

Several studies have suggested that physicians may underrecognize symptoms that trouble their patients and that patient-reported outcome measures were more likely to reveal serious toxic effects than clinician reports [26, 257, 258]. In the trial, NRG1203,[259] clinicians were found to have substantially underreported symptomatic gastrointestinal adverse events compared with patients themselves, with important implications for the primary outcome of the research. However, others have shown higher levels of agreement between physician-reported and patient-reported outcomes [260]. Our findings showed a large discrepancy in the rating of adverse events between CROs and PROs. Patients reported significantly more adverse events at all time points, suggesting CROs may not capture the real range of side effects for patients. Previous studies have also shown the potential for physician under-reporting of toxicity, possibly due to the lack of reporting of side effects not felt directly attributable to radiotherapy [261, 262]. This could

apply to our cohort, in which 35% initially underwent hormonotherapy and 35% concurrent chemotherapy.

Association Between Patients' Demographics and Reported Adverse Events

Using predictive factors of clinical radiosensitivity, such as age and BMI, can help identify patients at risk of complications and initiate appropriate therapy. In our study, there was no statistically significant association between baseline patient characteristics and reported toxicities. In contradiction to some of the literature, as there are many studies that say that these factors increase RT toxicity, our study aligns more with the literature that does not find an association between clinical factors such as age, diabetes, hypertension, and smoking and significantly increased pelvic radiation acute toxicity [263-266]. For example, total treatment time and dose per fraction have not been reported to be related to acute bladder injury [264, 267]. Also, in some studies, chemotherapy administered concurrently with radiation therapy has not been shown to significantly increase the risk of acute bladder complications [192, 265, 268]. In contrast, some studies reported that hormonal therapy in prostate cancer has been associated with more acute genitourinary complications [266]. While other studies have shown that low BMI, female gender, and combined chemoradiation may increase the risk of radiation-induced enteritis [167, 192, 268-275].

The Usability of PROs in Patient Triage

Suboptimal management of acute AEs associated with pelvic radiotherapy contributes to higher healthcare use and poorer outcomes [18, 276, 277]. If the incidence of severe AEs in patients can be predicted, a targeted clinical preventative intervention can be adopted with the intention of significantly reducing the severity of side effects related to pelvic radiotherapy. In this study, we found no evidence of predictable outcomes, such as emergency room visits and hospitalizations.

This was not surprising, though, as our data showed very few patients had moderate or marked treatment-related adverse events, which might lead to such outcomes. The low overall prevalence of moderate/marked adverse events has been reported in several adjuvant radiotherapy trials [278-281]. However, previous studies examined intervention effects on symptoms in general [17, 276]. More studies with larger sample sizes are needed to uncover the impact of interventions and the timing of these interventions on such outcomes to enable robust models and reliable intervention effect estimates [282].

Strengths and limitations

Our study must be interpreted within the context of its strengths and limitations. One potential limitation of the study was that most participants had prostate cancer. Consequently, male predominance was noticed in the study sample. Also, further recruitment was not possible during the study period which led to a discrepancy between the actual number of participants and the intended sample size (n=102 vs. expected n=147). The smaller sample size means that a true association may not end up being statistically significant due to lower statistical power. Therefore, results that are “not significant” cannot be interpreted as meaning that there is no association between the two variables. Future research with a larger sample size is needed to confirm any associations. Selection bias may have occurred as only participants with internet access and possessing a smartphone were recruited, which may reflect educational level or socioeconomic status. The main limitation was that the validated clinician and patient questionnaires used slightly different questions and rating scales to ensure appropriate readability levels. However, it has been argued by some that variation was 'quite acceptable and comprehensible' due to the differences between toxicity scoring by patients and clinicians. For example, ePROs are not consistent with existing standardized metrics for adverse event reporting in clinical settings that use a single metric

for each adverse event, such as the CTCAE v.5; while CTCAE uses a three-point scale for urinary frequency and urgency together, ePROs separate these items and use a 5-point scale. Therefore, to enable a direct comparison with ePROs, the scales of both scoring systems have to be harmonized by taking the definitions of each point on their respective scale and merging them [283, 284]. Strengths of our study include the longitudinal examination of PROs with a high response rate and the integration into the clinic workflow. Since the patients completed their PROs responses on their own devices, there were no additional tasks required from the clinicians, allowing for reproducibility across many different clinical contexts.

CONCLUSION

In conclusion, this study confirmed that it was feasible to integrate ePROs during the course of radiotherapy. Patients report more adverse events compared with clinicians, in general, and concordance was poor between PROs and CROs. While no clinically significant associations were found between baseline characteristics and the occurrence of adverse events or specific health outcomes like medication changes, ER visits or hospitalization, larger future studies are needed to explore ePROs as a predictive tool.

STATEMENTS

Ethics Approval and Consent to Participate: This study protocol was reviewed and approved by the Research Ethics Board of the McGill University Health Center, and approval number **PROS / 2022-8347**. Written informed consent was obtained from participants to participate in the study.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Contributors' Statement Page

Dr. Joanne Alfieri conceptualized and designed the study and the data collection instruments, interpreted the results, and reviewed and revised all manuscript drafts for important intellectual content. Drs. Luis Souhami, Tarek Hijal and Talía Malagón helped interpret the results and critically reviewed the manuscript for important intellectual content. Dr. Rania Soliman conceptualized and designed the study, conducted the analyses, drafted the initial manuscript, revised the manuscript, and produced the final version.

All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Data Availability Statement

All data generated or analyzed during this study were included in this article [and/or] its supplementary material files. Further enquiries can be directed to the corresponding author.

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THESIS DISCUSSION

This prospective study investigates PROs reporting via mobile application in patients receiving pelvic radiotherapy for curative intent. The study aimed at and found that it is feasible to integrate ePROs so that patients find it usable and accept electronic reporting and evaluate the association between **PROs and CROs**. Also, we tried to investigate the association between patients' demographics and the reported symptoms and QoL and the usability of PROs in patients' triage.

The feasibility of collecting e-PROs via Opal

In our study, electronic reporting via the Opal application was feasible and conducted by almost all participants. However, the 56 patients declined, having a higher median age; non-participation was caused by a lack of resources like mobile phones or internet connection, not due to the lack of technological skills. Our response rate was >90% in eligible patients. While there was no scientifically proven minimum response rate, 60% has been used by some as a measure of survey quality [285]. Reasons why patients declined to answer the questionnaires were not documented. We speculate the reasons were partly related to its 28-question length. This would be consistent with implementation issues (e.g., 20-question limit) previously described in the literature [277]. Given our findings, we would recommend questions be considered in a tree-format questionnaire to reduce completion times and improve uptake. Patients in our study who were age 70 or older, which represented almost half of the study population, had worse compliance to completion of questionnaires than the patients below 70. This was supported by previous findings that younger patients use ePROs more readily data [225, 231, 286, 287]. Slightly decreased response rates during follow-up were expected as compliance was higher during active treatment than after treatment [231, 287]. We chose to use

electronic reminders via the application, a retention strategy shown to enhance participants' adherence during treatment and follow-up in previous studies [288].

First, this study depended on the participants using *Opal* on their own devices. Adherence to PROs completion in the app was high despite the fact that no clinician feedback on the responses was provided. One reason might be that the app was already well implemented in the radiotherapy department and was introduced to all patients. The average adherence to PROs completion was higher than in previous findings, where the median age was 2–12 years below the median age of this study [225, 231, 287].

Overall, the high completion rates indicate that ePRO reporting using the Opal application was easy for patients to use. Thus, initial user acceptance was high, and some even reported that it served as a reminder for reporting symptoms and side effects like previous findings with ePRO in cancer care [289].

Association Between PROs and CROs

Although this analysis found few patients had moderate/marked AEs, overall clinician-reported GI and GU toxicity rates were comparable to clinician-reported outcomes in the literature [290-292].

We know that patients report more adverse events than clinicians [262, 293-299]; therefore, without PROs, the prevalence of adverse events may be underestimated. However, there were some that have shown higher levels of agreement between physician-reported and patient-reported outcomes [260]. Our findings showed a large discrepancy in the rating of adverse events between CROs and PROs. Patients reported significantly more adverse events at all time points, suggesting CROs may not capture the important changes for patients. Previous studies have also shown the potential for physician under-reporting of toxicity, possibly due to the lack of

reporting of side effects not felt directly attributable to radiotherapy [261, 262]. This could apply to our cohort, in which 35% initially underwent hormonotherapy and 35% concurrent chemotherapy.

We have discussed whether PROs could potentially replace CROs to assess adverse events of pelvic radiotherapy. Broadly, patients rate their subjective satisfaction with an experience of a range of changes, while clinicians seek objective adverse treatment effects. Therefore, We acknowledge CROs are still widely used, but we support the alternative viewpoint that both PROs and CROs may be necessary as they measure different aspects of disease experience and are complementary [300].

Association Between Patient Demographics and Reported Adverse Events

Using predictive factors of clinical radiosensitivity like age and BMI can help identify patients at risk of complications and initiate appropriate therapy. In contradiction to some of the literature, as there are many studies that say that these factors increase RT toxicity, our study aligns more with the literature that does not find a statistically significant influence of baseline patient characteristics on reported toxicities [263-266]. Other studies have shown that low BMI, female gender, and combined chemoradiation may increase the risk of radiation-induced enteritis [167, 192, 268-275].

The Usability of PROs in Patient Triage

Acute AEs associated with pelvic radiotherapy can significantly degrade patients' quality of life. They may lead to radiotherapy intolerance or termination of radiotherapy, which negatively impacts the therapeutic effect and can be life-threatening to the patient in some cases [18, 276, 277]. Furthermore, accurate prediction of AEs is essential for individualizing and optimizing radiotherapy plans [301, 302]. Therefore, it is essential to establish a method for rapidly

assessing AEs based on available clinical data [301]. The use of PROs can enable early identification of symptoms. It may facilitate timely interventions to improve symptom management and avoid serious complications [303, 304]. In this study, we examined clinical patient outcomes, including modification of medications, ER visits, and hospitalizations, to assess the ability of using PROs scores to predict the occurrence of such outcomes in patients receiving pelvic radiotherapy. We found no evidence of association among them. This was not surprising, given that our data showed very few moderate/marked treatment-related adverse events, which may lead to such outcomes. The low overall incidence of moderate/marked adverse events has been reported in several adjuvant radiotherapy trials; typically, there are less than 10% grade 3 GI and less than 5% grade 3 GU CTCAE toxicity [278-281].

Strength And Limitations

Our study must be interpreted within the context of its strengths and limitations.

Given the rarity of significant GI or GU toxicity events, our sample size was insufficient to build a strong predictive model for toxicity. One potential limitation of the study was that most participants had prostate cancer. Consequently, male predominance was noticed in the study sample. Further recruitment was not possible in the study period; however, the total intended sample size was almost reached.

Selection bias may have occurred when we recruited only participants based on internet access and having a smartphone, reflecting educational or socioeconomic status. Certain patient groups may not wish to participate in a PROs study, resulting in a trial population unrepresentative of the general population. In our study, participants who declined participation in the PROs study were slightly older than those who participated.

We chose to administer the questionnaires and arranged for a follow-up visit with the clinician at 2 weeks after treatment which is not part of routine care, and the clinician would likely be aware of the study participation. We wanted to capture the remaining acute symptoms reported by the patient after treatment, which usually resolves within three weeks after radiotherapy [158], however, this has disrupted the effectiveness of the blinding process and potentially influenced study outcomes.

In addition, the questionnaire was able to follow acute toxicity patterns across different primary tumour sites. However, depending on the site, variability in the questionnaires may have been more appropriate, as not all side effects were captured (e.g., skin toxicity).

The main limitation was that the clinician and patients were asked slightly different questions using different comparators with various subscales; PROs are not consistent with existing standardized metrics for adverse event reporting in clinical settings that use a single metric for each adverse event, such as the CTCAE v.5; also, while CTCAE uses a single scale for urinary frequency and urgency together, PROs separate these items and use a 5-point scale.

To enable a direct comparison with PROs, the scales of both scoring systems were harmonized according to a defined algorithm. The same grading algorithm was applied across all adverse events, rather than tailoring the algorithm for each adverse event. An alternative approach varying the algorithm between different adverse events could be used; however, varying the algorithm would add substantial complexity and risk of errors in analyses, and would likely be infeasible to evaluate quantitatively given the large amounts of necessary data to do so. Future approaches aim to refine or confirm the algorithm, would improve our understanding of patient and clinician ratings, and assist clinicians and policymakers with interpreting clinical trial results.

Also, varying levels of experience in grading toxicity between clinicians can lead to interobserver variability; there was no formal training protocol for clinicians assessing adverse effects in our study.

Strengths of our study include the longitudinal examination of PROs with a high response rate and the integration into the clinic workflow. Since the patients completed their PROs responses on their own devices, there were no additional tasks required from the clinicians, allowing for reproducibility across many different clinical contexts.

CONCLUSION:

In conclusion, this study confirmed that it is feasible to integrate ePROs during the course of radiotherapy. Patients report more adverse events compared with clinicians, in general, and concordance was poor between PROs and CROs. While no clinically significant associations were found between baseline characteristics and the occurrence of adverse events or specific health outcomes like medication changes, ER visits or hospitalization, larger future studies are needed to explore ePROs as a predictive tool.

FUTURE DIRECTIONS:

Pelvic radiation adverse events are multifactorial. Several risk factors and subgroups of patients at increased risk of developing radiation-induced toxicity have been identified [305]. A minority of oncology practitioners have integrated PROs with clinician feedback, even though previous studies found that communication and quality of care could be improved when the patients felt their information was used by the clinicians [33, 289, 306].

Further studies should be performed to improve the literature concerning this issue, focusing on identifying subgroups of patients for which a preventive strategy should be advised.

In some ePRO solutions today, advice is provided to the patient via the app or website [212]. The weekly contact between patients and clinicians during radiotherapy makes it easy to make ePROs an integral part of care [210]. It was possible and relevant to monitor severe or worsened symptoms the day after ePRO completion and use the disease- and treatment-specific PROs as a communication tool to potentially intervene earlier and improve the patient's physical quality of life [21, 306]. In future studies, we recommend that patients and caregivers receive real-time feedback to be meaningful and to be reassured if their symptoms are as expected.

We also recommend future larger studies aiming to use PROs in providing more complex, adaptive care, such as early side effect management to mitigate severe toxicity, potentially modifying radiation delivery while on treatment, and better evaluating how treatment modifications may affect patient outcomes on a broader level (e.g., dosimetric changes, brachytherapy, concurrent systemic therapy) [307-309].

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