

## Review

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# Pursuing Quality in the Application of Bladder Cancer Quality of Life Research

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**Abstract.** Patient-reported outcomes (PRO), including health-related quality of life (HRQOL) measures, represent important means for evaluating patients' health outcomes and for guiding health care decisions made by patients, practitioners, investigators, and policy makers. In spite of the large number of studies examining HRQOL in patients with bladder cancer, very few review articles investigated this topic. Because these review studies report mixed results, incorporating bladder cancer HRQOL measures into standard urological practice is not a viable option. In this non-systematic review of the literature and commentary we note some general concerns regarding PRO research, but our primary focus is on the HRQOL methodology within the context of two types of bladder cancer: muscle invasive and non-muscle invasive bladder cancer. Considering bladder cancer HRQOL as the interaction of four areas of the assessment process (i.e., what model of HRQOL to choose, what instruments are available to fit the choice, how interpretation of the resulting data fits the model, and how to derive some utility from the chosen model) and the two types of disease (i.e., muscle invasive and non-muscle invasive) may move us toward a better understanding of bladder cancer HRQOL. Establishing a useful model of perceived general health or specific symptoms is the first and most important step in developing the responsive bladder cancer HRQOL measures necessitated by clinical settings.

**Keywords:** Patient-reported outcomes, health-related quality of life, bladder cancer, muscle invasive bladder cancer, non-muscle invasive bladder cancer, quality of life assessments, conceptual model of quality of life, design and development of bladder cancer quality of life measures

## INTRODUCTION

Patient-reported outcomes (PRO), including quality of life (QOL), represent the experiences of patients and become a means of guiding health care decisions

made by practitioners, investigators, and policy makers [1]. QOL is a complex, multifaceted concept that continues to defy consensual definition. The term health-related quality of life (HRQOL) is primarily used in the field of medicine where health is often viewed as incongruous with disease [2]. HRQOL is a subjective sense of well-being encompassing physical, psychological, social, and spiritual dimensions [2–5]. A large number of studies have examined HRQOL in patients with bladder cancer.

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Bladder cancer is a heterogeneous disease, with low-risk non-muscle invasive bladder cancer (NMIBC: stage Ta, T1, and carcinoma in situ or CIS) akin to a chronic disease, but clinically localized muscle-invasive bladder cancer (MIBC:  $\geq T2$ ) often following a deadly course [6]. This spectrum of disease requires a range of treatment modalities, all of which may impact patients' perceptions of HRQOL [7].

NMIBC accounts for about 80% of all bladder cancers [8]. In addition to differences in prevalence and molecular pathogenesis that yield markedly different capacities for growth and metastasis [9], NMIBC and MIBC management and follow-up care also differ substantially (e.g., transurethral resection of bladder tumor with or without adjuvant intravesical therapy for NMIBC; and radical cystectomy and urinary diversion for MIBC and high-risk NMIBC refractory to conservative therapy) [10–12]. Accordingly, substantial differences may exist in how NMIBC and MIBC affect patients' HRQOL.

The HRQOL in the context of NMIBC is generally understudied, but the few studies in this patient population demonstrate advantages in HRQOL compared to patients treated for MIBC despite the reported bother with NMIBC treatment side effects (e.g., pain, discomfort, voiding problems, infection) [10–12]. Studies that examined the impact of adjuvant and neoadjuvant chemotherapy in MIBC patients showed frequent reports of bothersome side effects including fatigue, nausea, vomiting, diarrhea, urinary discomfort (e.g., cystitis, pain during urination, bladder spasm, urinary urgency), and increased sexual problems (e.g., vaginal dryness among women, and erectile dysfunction among men) [10–13]. The impact of cystectomy and urinary diversion on MIBC patients' HRQOL is well documented (e.g., body image, urinary incontinence and leakage, sexual dysfunction, and bother with self-catheterization) [3–5, 14–20].

Although several comparative studies have attempted to examine the heterogeneous effects of different bladder cancer treatment modalities on a patient's HRQOL, few systematic reviews on HRQOL currently exist to guide research and practice in this area, and those that do exist, report mixed findings [3–6, 14–21].

In this broad, non-systematic review of the literature and commentary we note some of the general concerns of HRQOL research, but our primary focus is on the interaction of HRQOL methodology and type of bladder cancer: NMIBC and MIBC. For our

discussion of bladder cancer HRQOL we focus on: a) what model of HRQOL to choose, b) what instruments are available to fit the choice and how well they function within a model, c) how interpretation of the resulting data fits the model, and d) how to derive some utility from the chosen model.

#### *Modeling concerns: What model of HRQOL to choose?*

Because HRQOL is a complex, multifaceted construct, a variety of conceptual models were used to guide HRQOL research. A conceptual model is a schematic representation of a theory that acts as a heuristic map to provide a better understanding of a phenomenon (e.g., HRQOL) by depicting interrelationships among concepts or domains (e.g., physical, psychological, social, and emotional functioning) [12–13]. Models are important in HRQOL research because they determine how the construct is conceptualized, and can be assessed, and evaluated.

Bakas et al. [10] examined 100 English language papers published between January 1, 1999 and August 31, 2010 pertaining to HRQOL models in different patient populations. These papers included literature reviews, instrument-development studies, descriptive or correlational studies, and intervention-based studies. Their study revealed that most of the HRQOL models described in these papers focused primarily on the influence of symptoms of various index conditions, rather than their management. Their study also revealed a large variation in the terminology and assessment of HRQOL, thus contributing to the difficulty in cross-study comparisons.

To address these limitations, Bakas et al. utilized a set of ten criteria [22] to develop recommendations for three distinct HRQOL models. Two of these three models apply primarily to individuals' HRQOL (see Wilson and Cleary [23], and Ferrans et al. [24]); the third model is a generic QOL model that applies to individuals, families, communities, populations and cultures (see World Health Organization International Classification of Functioning, Disability, and Health model; WHO ICF [25]).

Bakas et al., recommend the individual model of HRQOL developed by Wilson and Cleary as it includes five well-defined domains: biological, symptoms, function, general health perception and overall QOL. Two less well-defined domains also exist in this model (i.e., individual and environmental characteristics). According to Bakas et al., the

domains of this model relate to one another, reciprocal relationships among the different domains may exist, and both environmental and individual factors are associated with outcomes, thereby affecting total HRQOL. They also recommend Ferrans et al.'s model as a revision of the Wilson and Cleary model, as it retains the five major domains of the original model, makes explicit the individual and environmental characteristics, and simplifies the Wilson and Cleary model by removing non-medical factors. Finally, they recommend the WHO ICF model because its main concepts are well-defined (i.e., encompassing perception of general health, health-related domains of well-being, with general health and health-related domains further conceptualized in terms of functioning within the model). However, according to Bakas et al., the WHO ICF's model is more appropriate as a mapping and classification framework than as a guide for hypothesis generation in HRQOL research compared to the models proposed by Wilson and Cleary [23] and Ferrans [24].

Although the Bakas et al. study reflects ten years of research on HRQOL, the authors concluded that further refinement of HRQOL models used in research is needed. According to Bakas et al., analyzing uniquely derived HRQOL models may provide distinctive domains that might further inform commonly used models. Likewise, while the United Kingdom's National Institute for Health and Care Excellence (UKNIHCE) recommends the use of global HRQOL measures, the UKNIHCE concludes that data may not be available or appropriate for all health conditions [26]. This is an important caveat because the use of global HRQOL measures implies that, across diseases, changes in HRQOL scores reflect changes in how various patients respond to the items on a HRQOL questionnaire. Additionally, the inherent ways to weigh different items in researcher-assessed HRQOL may further bias the interpretation of these measures especially when patients' specific values or symptoms change over time [27].

Patients' responses to items on a HRQOL measure may vary greatly given the nature of a disease or a treatment when the HRQOL measure incorporates a variety of symptoms. For example, if some patients treated with chemotherapy experience fatigue but no pain, whilst other patients treated with surgery have no fatigue but do experience pain, these two items might be uncorrelated with each other — or even negatively correlated — and yet both items

could be strong predictors for HRQOL [28]. These issues emphasize the importance of having “bolt on,” disease-specific subscales attached to a global HRQOL measure when studying a specific disease or treatment option [29]. If not assessed, clinically important HRQOL signs and symptoms may go unreported—and, in a clinical setting, untreated [30]. Thus, a failure to characterize a HRQOL model adequately, beginning at the point of its definition may lead to a mismatch between the conceptual model and its application in clinical settings [28].

In sum, models are important in PRO research as they determine how the HRQOL constructs are conceptualized. Accurately representing the breadth of clinically significant symptoms and changes in functioning following MIBC and NMIBC treatment are necessary so that indicators of low levels of HRQOL are not overlooked by health care providers.

*Instrument concerns: How well the instrument of choice function within a selected mode?*

Having settled on a model of HRQOL in clinical bladder cancer care, the next step is to develop or select a measurement instrument. Placing PRO-based variables at the center of research and clinical trials makes accurate measurement a cornerstone of HRQOL in clinical care [30, 31]. There are a multitude of PRO measures of HRQOL and some useful guidelines for using reviews to choose among the available instruments as well as recommendations for working with patients with low levels of health-literacy, socially excluded, and non-English speaking patients (see Boynton et al. 2004) [30]. Table 1 depicts examples of HRQOL measures currently used in bladder cancer research.

One method for choosing a HRQOL measurement instrument is to make a selection from among a set of instruments previously vetted by researchers. The Clinimetrics working group of the EMGO Institute of Health and Care Research of the VU University Medical Center in Amsterdam developed COSMIN, a checklist created to reconcile approaches to evaluating measurement instruments [31–32]. Beginning with a four-round Delphi study of 57 international experts (psychologists, epidemiologists, statisticians and clinicians), the COSMIN group developed a standardized tool that appraises three measurement domains: 1) reliability (internal consistency, reliability, and measurement error); 2) validity (content validity, construct validity and criterion validity), and; 3) responsiveness (the ability to detect change

Table 1  
Quality-of-Life Instruments (modified from Mohamed et al.) [40]

Instrument	Institution	Domains	Validated	Reliable	Cancer specific	Bladder cancer specific	No of items	Publicly available
BCI [29]	University of Michigan	Urinary Bowel	Yes	Yes	Yes	Yes	34	No
FACT-VCI [30]	Vanderbilt University	Sexual function See FACT-G Urinary Bowel	Yes	Yes	Yes	Yes (limited to cystectomy)	45	Yes
QLQ-BLM 30 Module [69]	EORTC	Sexual function Urinary Bowel	Ongoing studies	Ongoing studies	Yes	Yes (muscle-invasive disease)	30	No
QLQ-BLS 24 Module [70]	EORTC	Sexual function Urinary Bowel	Ongoing studies	Ongoing studies	Yes	Yes (non muscle-invasive disease)	24	No
FACT-BL [71]	FACIT	Sexual function See FACT-G Limited Urinary Limited Bowel	Ongoing studies	Ongoing studies	Yes	Yes	39	Yes
FACT-G [72]	FACIT	Physical Social Emotion Function	Yes	Yes	Yes	No	27	Yes
QLQ-C30 [56]	EORTC	5 Functional Scales 3 Symptom Scales	Yes	Yes	Yes	No	30	No
SF-36 [73]	RAND	1 Global Health / QOL scale 8 Domains Including Physical Mental Social function Emotional	Yes	Yes	No	No	36	Yes

Note: BCI: Bladder Cancer Index; EORTC: European Organization for the Research and Treatment of Cancer; FACIT: The Functional Assessment of Chronic Illness Therapy; FACT-BL: Functional Assessment of Cancer Therapy – Bladder Cancer (Extension of the FACT-G+12 additional bladder cancer specific items including incontinence, diarrhea, body image, sexual function, and stoma care); FACT-G: Functional Assessment of Cancer Therapy – General; FACT-VCI: Functional Assessment of Cancer Therapy – Vanderbilt Cystectomy Index (Extension of the FACT-G+17 additional bladder cancer and treatment specific items); QLQ-C30: EORTC Quality-of-Life Core Questionnaire; QLQ-BLM30: EORTC Quality-of-Life Core Questionnaire – Bladder Cancer Muscle Invasive (Extension of the QLQ-C30+30 additional bladder cancer specific items; <http://www.eortc.be/home/qol/modules.htm>); QLQ-BLS 24: EORTC Quality-of-Life Core Questionnaire – Bladder Cancer Superficial (Extension of the QLQ-C30+24 additional bladder cancer specific items; <http://www.eortc.be/home/qol/modules.htm>); RAND Corporation: Research AND Development SF-36: Medical Outcomes Study 36-Item Short Form.

over time) [31–33]. In addition, the COSMIN checklist includes items related to interpretability and generalizability of HRQOL measurements. Both classical and item response test theories can be assessed with this checklist. The COSMIN group also provided a database of systematic reviews of studies that utilized HRQOL instruments in different populations which is available at the COSMIN web-site <http://database.cosmin.nl/>.

Another approach to evaluating HRQOL measures comes from a study conducted by the International Society for Quality of Life Research (ISOQOL) [34]. Measurement standards in this approach include: 1) documentation of the conceptual and measurement model; 2) evidence for reliability, validity (content validity, construct validity, responsiveness); 3) interpretability of scores; quality translation, and; 4) acceptable patient and investigator burden.

Besides attending to the measurement properties of a preexisting bladder cancer HRQOL assessment instrument, making a choice among the available options requires an awareness of the assumptions measurement experts make in their own model selection process – especially when selecting a disease-specific measure. There are more than 50 published studies of HRQOL in bladder cancer using over a dozen instruments [3–5, 14–20, 35]. Different methods for selecting items for a disease-specific (i.e., MIBC or NMIBC) HRQOL questionnaire produce different instruments. Homogeneous sets of items produced by psychometric strategies can produce scales that do not include important patient concerns [36, 37]. Scales that include a variety of uncorrelated items may capture a greater number of patient concerns. Such “clinimetric” scales combine a variety of items that may not relate to each other statistically [38].

#### *Muscle invasive bladder cancer (MIBC)*

Most validated bladder cancer HRQOL measures, whether psychometric or clinimetric, utilize a model that fits patients with MIBC. Patients treated with radical cystectomy (RC) comprise the research samples, and the question addressed in developing or testing the measure was whether one type of urinary diversion, as compared to other urinary diversion types, significantly reduces patients’ HRQOL. Reviews of data from such studies generally find that the type of urinary diversion is not a consistent predictor of HRQOL, independent of the HRQOL measure chosen. A recent study utilizing a psychometri-

cally developed scale serves as an example [35]. The Vanderbilt Cystectomy Index (the FACT-VCI) [35] is a combination of the 45-item Functional Assessment of Cancer Therapy (FACT)-General scale, plus 17 added items designed to measure post-cystectomy HRQOL. Prospective comparison between open radical cystectomy and robot-assisted laparoscopic cystectomy, with the FACT-VCI administered preoperatively and at 3, 6, 9 and 12 months post-operatively, resulted in findings of no significant differences in HRQOL outcomes, and HRQOL in both cohorts returning to baseline three months after surgery.

Even among studies using disease-specific HRQOL measures however, the measurement model affects outcome conclusions. The Bladder Cancer Index (BCI) is disease-specific HRQOL instrument that consists of 34 items [29]. However, its conceptual model utilizes three primary domains (urinary, bowel and sexual health), and two sub-domains (function and bother) for each primary domain. In a study comparing patients managed with various treatment modalities, some differences between HRQOL arose, e.g. urinary function scores were significantly lower among cystectomy patients treated with a neobladder urinary diversion compared with those in other treatment groups, including the cystectomy/ileal conduit group [29].

#### *Non-muscle invasive bladder cancer (NMIBC)*

Singer et al. point out the rarity of NMIBC HRQOL research studies, suggesting that the sparse literature on NMIBC patients implies that their HRQOL is comparable to that of the general population [37]. Their research on NMIBC patients receiving intravesical instillation of bacillus Calmette-Guerin (BCG) does show that specific BCG side effects do not seriously impair satisfaction with life. However, this was a short-term study, limited to the six weeks of BCG treatment.

In contrast, a one-year multi-center, prospective study of patients with NMIBC reported differences in HRQOL [38]. Participants in this study included cancer stages 0a (papillary carcinoma), 0is (carcinoma in situ) and I who self-completed HRQOL questionnaires during the diagnostic process (baseline), and then six and 12 months later. The sample consisted of 244 NMIBC patients undergoing transurethral resection, with or without intravesical therapy. Men made up the majority of the sample (84%). The average age was 70 years. About 40% of the sample had diagnoses of papillary stage bladder cancer (0a). Approximately

60% of the sample received transurethral resection only, and about a third received resection combined with BCG or mitomycin-C. During follow-up, 63 patients showed evidence of cancer recurrence, progression, or metastasis. Of the original sample 13% were in complete remission at 12 months.

Both global HRQOL and disease-specific HRQOL questionnaires including Version 2 of the Health Survey Short Form-36, and the BCI have been used. Physical health measured with the SF-36 was comparable to an age-referenced US population group at baseline and during the 12-month follow-up. Mental health data, per the SF-36, revealed significantly lower scores at baseline and at the six-month but not at the 12-month follow-up compared to the reference population. The BCI showed significant urinary improvement from diagnosis to 12-month evaluation, and stable bowel domain. From baseline to 12-month follow-up sexual function scores decreased from 40.4 to 34.6, but sexual bother scores remained stable. A statistically significant difference by tumor stage interaction was found in the BCI sexual summary. Patients diagnosed at stage 0a improved, but those at stage I deteriorated. Almost half of the patients with no sexual problems at baseline had worsened at 12 months. The impact of the NIMBC diagnosis on mental health was apparent at six months following diagnosis emphasizing the need to incorporate psychological care aspects into the management of patients with bladder cancer [39].

In the study reporting the utility of the BCI, urinary function scores, urinary, bowel, and sexual scores did vary between the native bladder groups, but the differences were not significant [29]. HRQOL measurements in that study, however, were administered at a median of 2.9 years following bladder cancer treatment. Accordingly, early differences between the native-bladder groups might not have been seen.

*In summary*, most of the research with bladder cancer assessed the impacts of various MIBC treatment options on HRQOL. Those studies generally revealed little difference in HRQOL outcome. For NMIBC, there may be a time-limited effect of the disease on mental health. However, this result is reported by a single study. Similar to other cancer populations, the clinical trajectory of bladder cancer (i.e., from diagnosis to survivorship) may be accompanied with change in mental health (e.g., depression and anxiety) as patients learn to cope with cancer and treatment outcomes. Long-term symptoms can decrease HRQOL in different groups of bladder cancer patients to an extent that makes it difficult to capture

with one generic questionnaire, further strengthens the idea to work clinimetrically with tailored atomized questions [28]. To optimize health care provision and the well-being of patients and survivors, clinical HRQOL measures must be sensitive to changes in symptoms and psychosocial needs as they rise.

*Interpretation concerns: How interpretation of the resulting data fits the model?*

Translating research from the findings of aggregate sample and population studies requires a change in perspective from groups to the individual. Osoba et al. put the issue succinctly: "Small numerical differences in mean scores derived from health-related quality-of-life . . . assessment instruments may reflect statistically significant results when large samples of subjects are involved, but the clinical interpretation of the meaning of small numerical differences is uncertain" [41].

One way to achieve translation of group data to clinic-based individual assessment is to combine group data and clinical assessments. Cella et al. used item-bank responses collected from 840 cancer patients to develop symptom vignettes across a range of symptom severity [42]. They then had clinical experts rank order the vignettes by severity, eventually arriving at a consensus regarding which two vignettes were at the upper and lower boundaries of normal and mildly symptomatic for each symptom. Using this process repeatedly, they identified cut scores separating mildly from moderately symptomatic, and moderately from severely symptomatic scores. The study yielded T-score thresholds that differentiated levels of symptom severity for pain interference, fatigue, anxiety, and depression based on a combination of clinical judgment and self-reported patient severity scores.

Other methods of turning group data into information for ranking individual HRQOL scores involve boot-strapping information from large groups of patients, while using that information to adapt or revise a HRQOL instrument to a clinical need. This is a process similar to that used by Cella et al. [42] but on a larger scale.

Hjollund et al. describe a generic PRO system, WestChronic, that boot-straps large quantities of individual data into new HRQOL areas. Developed in Denmark in 2004 for epidemiological research, this system allows clinicians to access PRO data on symptoms, functional status, and other indicators of

HRQOL [7]. In a recent report on the system, 22 PRO projects existed for 18 diagnostic groups, and available data included 59,232 questionnaires from 30,174 patients. Although none of the reported projects included bladder cancer patients, projects existed for lung and prostate cancer. In line with recommendations on the design and evaluation of outcome measurements [30], the authors reported a four-step process for the development of specific-disease measurements: 1) identifying HRQOL content – specific content is identified through literature reviews, interviews with patients, and input from content experts such as clinicians and nurses; 2) questionnaire development– questionnaire items are written, again based on information from literature reviews, patient interviews and content experts; 3) patient interviews – testing the draft questionnaire determines if the meaning and intention of each question is understood by patients, and; 4) testing – the questionnaire is administered to a large sample of patients and analyzed to test the statistical properties, including validity, reliability, sensitivity and responsiveness. Using this process it is possible to enable clinical access to PRO data on symptoms, functional status, and health-related quality of life of individual patients. This allows clinicians to flag symptoms that need further attention during a patient visit. In summary, combining group data with clinical assessments provides a work-around for the difficulties inherent in translating research from the findings of aggregate sample and population studies into a format useful for clinical care. This process requires a systematic approach to creating HRQOL instruments, a large amount of data and a good deal of expense.

*Utility concerns: How to derive some utility from the chosen model?*

Alston et al. surveyed a nationally representative sample of 1,068 patients who had seen at least one health care provider in the previous 12 months, and found four issues patients face regarding medical communication [43]: a) patients' desire to engage in shared health-care decision making, b) there is a gap between patients' desire for engagement in their health care and the usual process of decision making, communication, and patients' preferences, c) patients' needs to experience more coordinated health care, d) and engaged patients are more likely to report a better healthcare experience.

It is these types of concerns that POR and HRQOL measures seek to address [44]. However, if the

modeling, instrument and interpretation issues are not addressed by the HRQOL measures used, these goals cannot be met. Research on bladder cancer patients' HRQOL is making progress, but if the goal is to create a standard procedure for addressing engagement and outcome in clinical practice, then we are not there yet. Studies of MIBC do not provide sufficient information to clearly assist patients in choosing one form of urinary diversion over another following radical cystectomy, for example [40]. Studies in NMIBC rarely find any effects on HRQOL, despite suggestions in the literature that effects exist on mental health and sexual function [29].

To better understand how bladder cancer affects patients' HRQOL, we suggest returning to our conceptualizations of bladder cancer HRQOL models and instruments. The Bladder Cancer Index is effective in showing differences in patients managed with endoscopic, intravesical or radical surgical treatments [29]. Further enhancing this the model may improve understanding of HRQOL across the MIBC and NMIBC disease spectrum.

Schmidt et al. found that psychological distress increased when patients learned of their bladder cancer diagnosis. The impact of receiving the diagnosis lasted at least six months, but apparently not twelve months [38]. This suggests that a bladder cancer measure must be responsive enough to measure changes in psychological well-being over a period of at least six months. Adding a few more items to measure a psychological health domain, for example, might increase the responsiveness of the BCI [29] to both MIBC and NMIBC. This would mean having a new model of bladder cancer HRQOL: one that reasonably includes psychological as well as physiological impacts. Furthermore, the model would have to assume that psychological distress does not occur at extreme endpoints. Life events such as divorce or sudden unemployment following bladder cancer may introduce additional distress. Hassles or daily stressors (e.g., daily use of catheters and stoma appliances) experienced may be significant contributors to emotional distress for a period of time before the patient masters skills required for self-care.

Similarly, adding other constructs to our model of bladder cancer HRQOL may provide a better measure of the breadth of issues associated with this disease. Research in other cancer populations reported significant associations between fear of cancer recurrence or progression and HRQOL [45]. Although not well documented in the bladder cancer population, fear of cancer recurrence or progression is

likely to be triggered by frequent follow-up cancer and morbidity surveillance, thus further decreasing the patient's HRQOL. Therefore, a comprehensive model of bladder cancer HRQOL should address these psychological parameters.

Another component of the breadth of model issue lies in the unmet needs of bladder cancer patients. Unmet needs are problems experienced by a patient that are not addressed by the health-care provider, health care system or the patient's support network. Unmet needs may include the informational needs (e.g., information about treatment options and side effects, follow-up care), supportive care needs (e.g., physical, emotional, sexual, practical, and social needs) or spiritual needs a patient perceives as necessary to achieve optimal well-being [45]. Research with cancer populations other than bladder cancer shows high levels of unmet need related to provision of information, psychosocial support, practical assistance, and sexual issues, resulting in increased anxiety and poorer HRQOL. Very few studies examined these issues in bladder cancer patients [45].

Understanding potential associations between unmet needs and HRQOL in bladder cancer patients is very important as these associations could be influenced by several patient factors. A patient's low health literacy level for example could influence patient-provider communication, thus, leading to increased unmet informational needs and difficulties with self-care and symptom management. Similarly, a patient's cultural beliefs, expectations, and values could influence a patient's treatment decision making leading to potentially avoidable treatment side effects and dissatisfaction with health care (e.g., opting for a neobladder to avoid altered body image associated with an ileal conduit). Thus, understanding a patient's needs, treatment-related objectives, values, and cultural/religious beliefs is pivotal in reducing the patient's unmet needs and improving his/her HRQOL and satisfaction with health care.

In developing the concept of individualized HRQOL, Huebner et al. [46] asked patients to determine which objectives besides survival are relevant and should be achieved by treatment. Integrating this concept into bladder cancer HRQOL research points out the importance of understanding patient-specific values and preferences (i.e., clinimetric measures) for the development of disease-specific bladder cancer HRQOL measurement. Equally important is the need to identify a comprehensive HRQOL model of bladder cancer that takes into account the differential impact of the disease and treatment outcome on

patients' functioning and wellbeing. The development of a new bladder cancer HRQOL metric should follow recommended psychometric standards [30]. Establishing the theoretical model of perceived health or symptoms of interest is the first and most important step in developing bladder cancer models and HRQOL measures [47].

Bladder cancer models will not be comprehensive without addressing informal caregivers' emotional adjustment and unmet needs. Despite the fact that cancer presents a crisis for patients and their families, [48] research in bladder cancer HRQOL has focused almost exclusively on the patient's response and adjustment to the disease. Research in other cancer populations has shown that informal caregivers play a significant role in helping patients manage their disease and treatment [49]. Most informal caregivers assume their role with little or no formal preparation and training and have low self-efficacy for caregiving [50, 51]. Caregivers also frequently encounter communication difficulties with patients, which can adversely affect the coordination of care as well as the quality of their relationship and QOL [52, 53]. For example, even well-meaning caregivers may offer assistance in ways that are controlling or over-protective rather than supportive [54] and can engage in maladaptive communication (e.g., criticism, nagging) [55, 56] that can undermine the patient's emotional well-being and abilities to achieve self-care goals (e.g., learning skills needed for stoma care).

In addition to undertaking complex care tasks and providing emotional support, informal caregivers must cope with the grief and loss associated with their loved one's life threatening illness [57]. Often, they are reluctant to discuss their fears and concerns because they worry that doing so will distress the patient [58–60]. This not only exacerbates patient and caregiver distress, [58] but it may also affect the caregiver's ability to provide care (e.g., assist with the use of stomal appliances) [61]. Poorly managed symptoms have been attributed at least in part to inadequate coping and exhaustion on the part of the family caregiver in other cancer populations [62, 63]. Thus, understanding and addressing caregiver unmet needs for information and support in bladder cancer is not only essential for improving caregiver health and well-being [64–66], but also for improving the quality of patient care – particularly for bladder cancer patients managing symptoms, treatment side effects, and self-care requirements associated with cystectomy and urinary diversions [67–68].

## CONCLUSION

PROs, of which HRQOL is one of the most important aspects, represent important means for evaluating patients' health outcomes and for guiding health care decisions made by patients, practitioners, investigators, and policy makers. Limitations in bladder cancer HRQOL research methodology, models used, and the heterogeneity of the disease clinical characteristics, however, may lead to a reduced utility of HRQOL assessments in the clinical trial setting. The challenge remains to encourage more research effort focusing on establishing a comprehensive model of HRQOL that is sensitive to bladder cancer and treatment outcomes and can be used in clinical settings to improve patient care.

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## CONFLICT OF INTEREST

The authors have no conflict of interest to report.

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