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Quality of Life and Symptom Assessment in Randomized Clinical Trials of Bladder Cancer: A Systematic Review

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Abstract

Objectives—Patient-reported outcomes (PRO) help patients, caretakers, clinicians and policy makers make informed decisions regarding treatment effectiveness. Our objective was to assess the quality of PRO reporting and methodological strengths and weaknesses in randomized controlled trials (RCT) in bladder cancer.

Methods—A systematic literature search of bladder cancer RCT published between January 2004 and March 2014 was performed. Relevant studies were evaluated using a predetermined extraction form that included trial demographics, clinical and PRO characteristics, and standards of PRO reporting based on recommendations of the International Society for Quality of Life Research.

Results—Nine RCTs enrolling 1,237 patients were evaluated. All studies were in patients with non-metastatic disease. In 5 RCTs, a PRO was the primary endpoint. The majority of RCTs did not report the mode of administration of the PRO instrument or the methods of collecting data. No RCT addressed the statistical approaches for missing data.

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Financial Disclosures and Conflicts of Interest

None

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Conclusions—We found that few RCTs in bladder cancer report PRO as an outcome. Efforts to expand PRO reporting to more RCTs and improve the quality of PRO reporting according to recognized standards are necessary for facilitating clinical decision-making.

Keywords

bladder cancer; patient-reported outcomes; clinical trials; quality of life; clinical decision-making

1. Introduction

Bladder cancer is the 7th most common cancer in men worldwide, with an estimated total of 429,793 new cases and 165,068 deaths in 2012[1]. Bladder cancer is more common in the western world, and is the 6th most common cancer in the United States, accounting for an estimated 74,690 new cases and 15,580 deaths in 2014[2].

Approximately 30% of newly diagnosed patients will have muscle-invasive bladder cancer (MIBC), for which neoadjuvant chemotherapy and radical cystectomy with urinary diversion are considered the standard-of-care[3]. A subset of patients with non-muscle invasive bladder cancer (NMIBC) will progress to invasive disease while many others will have a protracted disease course that may include invasive monitoring and intravesical treatments[4].

For any stage of bladder cancer, informed decision-making needs to consider objective outcome measures with a high level of evidence as well as the patient's values and experience[5]. It is increasingly recognized that patient-reported outcomes (PRO) help patients, caretakers, clinicians and policy makers make decisions regarding treatment effectiveness[6; 7]. However, previous systematic reviews have noted several weaknesses in PRO studies in bladder cancer, including retrospective study design and use of non-validated questionnaires[8; 9]. Further, reviews in other cancers have shown poor PRO reporting in randomized controlled trials (RCT)[10; 11]. Therefore, standards for reporting PRO in RCTs have recently been established[12; 13]. The objective of this review was to identify the number of RCTs in bladder cancer that have included PRO as an endpoint, and to assess the quality of PRO reporting from these studies.

2. Materials and Methods

2.1. Search strategy and identification of studies

An electronic, systematic literature search using Pubmed/Medline, the Cochrane Library, PsycINFO and PsychARTICLES was used to identify RCTs in bladder cancer with a PRO component from January 2004 to March 2014. Details of our search strategy used in other cancers have been previously described[10; 11; 14]. We limited our search to the last 10 years because a previous MEDLINE search of the literature from 1966 to January 2004 found no RCT evaluating PRO after radical cystectomy[9]. Relevant studies listed as references were also considered.

2.2. Selection criteria

English-language RCTs involving adult patients with bladder cancer were included regardless of disease stage. Studies had to enroll at least 50 patients to be included. Studies of patients undergoing screening or involving patients with benign disease were excluded. Conference abstracts were not included. Interventions included any RCT comparing conventional treatments. Studies considering psychological intervention or complementary or alternative medicine were excluded. Any studies evaluating a PRO either as a primary or secondary outcome were included. This included both multidimensional HRQOL outcomes and any other type of PRO measuring the impact of an intervention. Studies evaluating only treatment adherence or satisfaction were not included.

2.3. Data extraction and type of information analyzed

Data were gathered through the Patient Reported Outcome Measurements Over Time IN Oncology (PROMOTION) Registry (<http://promotion.gimema.it>)[14]. For the purpose of this review, two broad types of information were extracted: 1) basic trial demographics and clinical and PRO characteristics; and 2) elements of PRO reporting based on recommendations from the International Society for Quality of Life Research (ISOQOL) [12].

3. Results

The systematic literature search yielded 1,682 records (Figure 1). After screening records, 58 full-text articles were assessed for eligibility of which 48 articles were excluded for being non-randomized (n=27), not including PRO (n=14), mixed sample (n=1), screening study (n=4), and non-English language (n=2). The result was 10 articles on 9 RCTs that met our study criteria enrolling 1,237 patients[15–24]. A summary of the main clinical results and PRO findings are presented in Table 1.

All 9 RCTs were performed in patients with non-metastatic disease: 5 in patients with NMIBC and 4 in patients with MIBC. In 5 RCTs, a PRO was the primary endpoint. The level of PRO reporting based on ISOQOL recommendations is presented in the Supplement Table.

Although 8 RCTs identified PRO as an endpoint in the abstract, only 2 stated a PRO hypothesis in the introduction. Seven RCTs did not report the mode of PRO administration or the methods of collecting data. A major limitation was the handling of missing data. None of the studies addressed the statistical approaches for missing data and only 1 stated the extent of, or the reasons for, missing data.

Four studies used versions of the EORTC instruments, and 3 studies used a bladder-specific instrument. However, 4 studies did not provide the rationale for choice of PRO instrument or evidence of PRO instrument validity.

Of the 5 RCT that used PRO as the primary endpoint, 3 described the limitations, generalizability and clinical significance of the PRO. All 5 interpreted the PRO in the discussion and discussed PRO in the context of other trial endpoints.

Two trials in patients undergoing radical cystectomy reported PRO differences. In a comparison of general plus epidural anesthesia versus general anesthesia alone, general plus epidural anesthesia was associated with improved pain control at all measured time points within 24 hours after surgery[21]. In a comparison of an early recovery after surgery protocol versus a conservative recovery regimen, patients treated with the early recovery protocol reported more favorable functioning and symptom scores on several EORTC measures on post-operative days 3, 7 and at discharge[18].

One study examined radiotherapy with and without chemotherapy for bladder-sparing treatment of MIBC. While this study met our inclusion criteria as a RCT of an intervention measuring PRO, this study did not report the instrument used, method or schedule of data collection, or PRO results[17].

Three of the 5 trials in NMIBC patients reported PRO differences. During transurethral resection of bladder tumors, fewer patients receiving spinal anesthesia with bupivacaine reported moderate or severe pain compared to patients receiving sufentanil[20]. However, bupivacaine was associated with intense motor blockade and longer time to recovery room discharge. A trial of oral anticholinergic therapy versus placebo during induction bacillus Calmette-Guerin (BCG) therapy reported more urinary and non-urinary symptoms with anticholinergic therapy with no clinical benefit[23]. In a comparison of gemcitabine versus one-third dose BCG for maintenance therapy, gemcitabine was associated with better functioning and symptoms on univariate but not multivariate analysis[16].

4. Discussion

Although bladder cancer is one of the most common cancers worldwide, there is paucity of evidence-based PRO from clinical trials. In the last decade, fewer than 1,300 bladder cancer patients were enrolled in a RCT evaluating PRO. Notably, 2 of these 9 studies focused primarily on anesthesia and peri-operative pain control rather than bladder cancer outcomes.

In contrast, a large number of RCTs with a PRO component have been conducted in prostate and gynecological cancers during a similar time period[10; 11]. Whereas we found no RCT in bladder cancer with robust PRO, in prostate and gynecological cancers the rate of high-quality PRO reporting likely to impact clinical decision-making was found to be 20% and 32%, respectively.

Historically, there have been few validated instruments in NMIBC or MIBC[8]. The EORTC QLQ-NMIBC24 was recently validated for use in clinical trials for intermediate and high-risk NMIBC[25]. This instrument was used by 1 of the 5 RCT in NMIBC we evaluated, while the other RCT used either ad hoc or generic cancer questionnaires. In MIBC, new instruments for evaluating the effects of radical cystectomy have recently been validated, including the Bladder Cancer Index and the Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy Index (FACT-VCI)[26; 27]. Only 1 MIBC study we evaluated used a bladder-specific questionnaire. Four of the 9 studies evaluated did not provide the rationale for PRO instrument used and 4 did not provide the validity or reliability of the instrument used. The purpose of disease-specific, validated questionnaires

is to capture PRO data meaningful to stakeholders for clinical decision-making. We believe that the dissemination of newer instruments will improve the quality of PRO reporting.

Much of the interest in PRO in bladder cancer has been comparing outcomes by urinary diversion type: ileal conduit, continent cutaneous or orthotopic neobladder. Understandably, there are no RCT comparing these diversions, and therefore, few RCT in MIBC. Prior to January 2004, there were no RCT evaluating PRO after radical cystectomy[9]. Of the 3 RCT we found in patients undergoing radical cystectomy, 1 examined techniques in orthotopic neobladder creation and 2 examined post-operative recovery and pain control.

Some of the weaknesses of PRO reporting in bladder cancer we found have previously been described[8; 9]. In the current review, only 3 studies reported baseline PRO data. Four studies did not provide the rationale for choice of the PRO instrument or the psychometric properties.

As in prostate and gynecological cancers, one of the main weaknesses of PRO reporting was in the handling of missing data.[10; 11] Missing data leads to reduced power and can be a significant source of bias. Missing data in PRO studies are often not random and can be associated with the outcome of interest. For example, patients completing a PRO survey after surgery may have considerable demographic and clinical differences compared to patients who chose not to complete the survey. The extent of missing data and the statistical handling of this data are, therefore, critical to understanding the generalizability of PRO findings.

This study highlights the current weaknesses of PRO reporting in bladder cancer RCTs. In contrast to previous systematic reviews, we used a formal, objective approach to evaluating PRO reporting in the bladder cancer literature. As has been demonstrated in similar reviews in prostate and gynecological cancers, high-quality PRO reporting can facilitate clinical decision-making and approval of beneficial interventions.[10; 11] When designing RCTs in bladder cancer, investigators should recognize the importance of including valid and reliable PROs in the trial protocol and the necessity for detailing the methodology of PRO assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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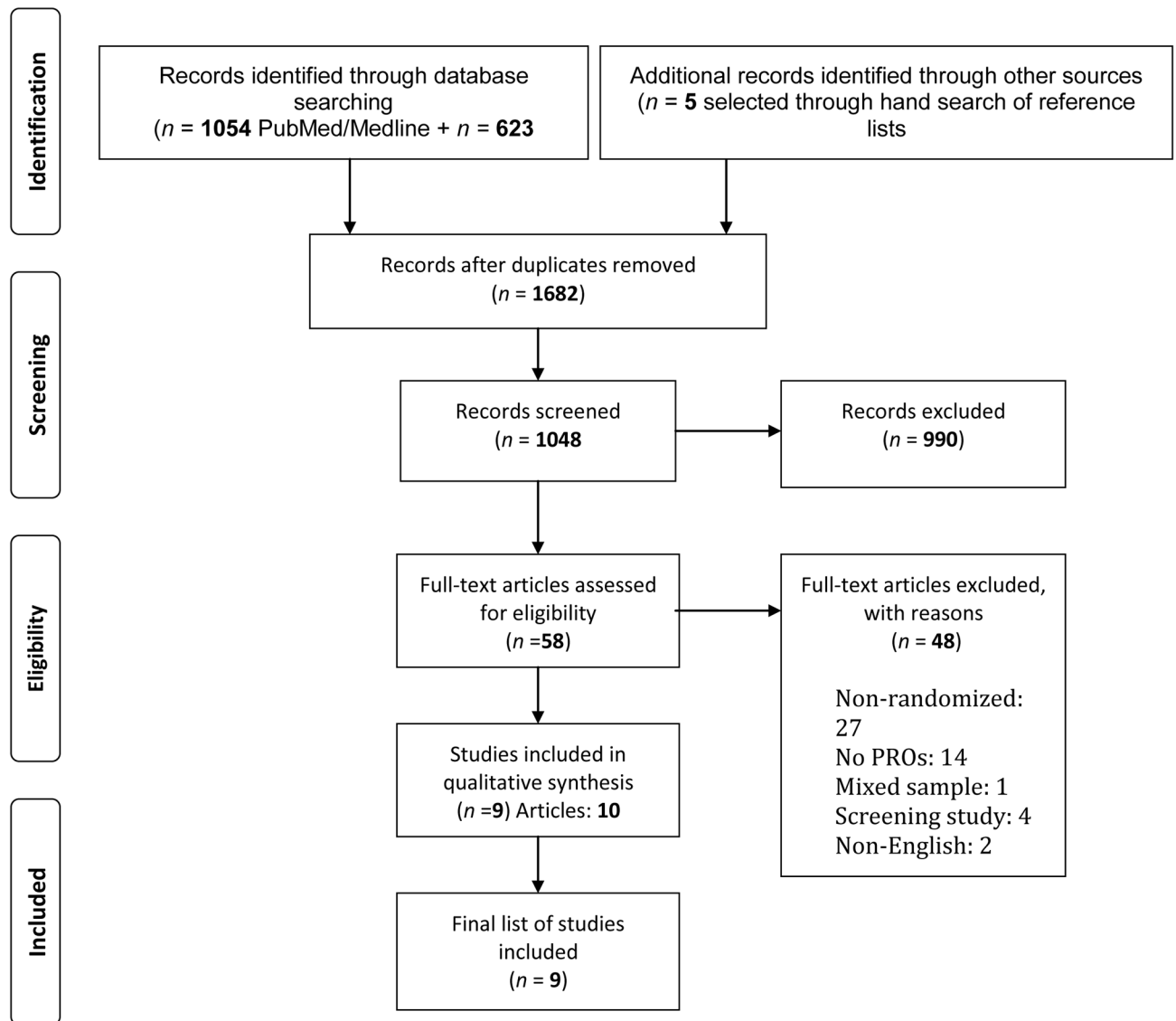


Figure 1. Schematic breakdown of literature search results of bladder randomized controlled trials (PRO= patient-reported outcomes).

Table 1

Randomized controlled trials with PRO design: basic study characteristics.

Study*	Overall study sample size	Baseline PRO sample size	PRO instruments used	Primary endpoint	Treatment outline	Summary of main clinical results	Summary of PRO results/PRO treatment recommendations
Gontero P et al. J Urol. 2013;190:857–862.	120	118	EORTC QLQ-C30 and EORTC QLQ-BLS24	PRO (including QoL or symptoms relief)	Intravesical gencitabine, 2000mg/50cc saline weekly for 6 weeks, maintenance once monthly for 1 year versus intravesical Connaught strain BCG 27mg/50cc saline (1/3 dose) weekly for 6 weeks, maintenance of 3 weekly treatments	Local and systemic side effects were more frequent in the BCG arm (56% vs 36%, p=0.03). The incidence of hematuria and fever were more common with BCG at T1 (post-induction), and dysuria was more common with BCG at T2	On univariate analysis, at T1, gencitabine arm had better cognitive and emotional functioning and urinary symptom distress. At T2, gencitabine arm had better cognitive functioning and less nausea and vomiting symptom distress.
James ND et al. N Engl J Med. 2012; 366:1477–88.	360	360	Not reported	Locoregional disease-free survival	55Gy or 64Gy radiotherapy to the bladder. Patients randomized to receive no additional therapy versus fluorouracil 500mg/m2 during fractions 1–5 and 16–20 plus mitomycin C 12mg/m2 on day 1	Radiotherapy with chemotherapy improved locoregional disease-free survival versus radiotherapy alone with no difference in adverse events or overall survival	Not reported
Ahmadi H et al. J Urol. 2013;189:1782–8 Skinner EC, Skinner DG. World J Urol. 2009;27:51–55.	295	179	Modified version of the Bladder Cancer Index	Renal function and anatomy at 3 years following surgery	Urinary diversion using Studer versus T-pouch ileal orthotopic neobladder	Not reported	No differences
Sabichi, AL et al. Cancer Prev Res. 2011;4,1580–1589.	146	146	EORTC QLQ C-30 (abbreviated form)	Time to recurrence	Celecoxib 200mg versus placebo twice daily for at least 12 months for a maximum of 24 months or until recurrence	No differences	No differences
Karl A et al. J Urol. 2014; 191:335–340.	101	101	EORTC QLQ-C30	PRO (including QOL or symptoms relief)	Following radical cystectomy, early recovery after surgery (ERAS) versus conservative post-operative treatment regimen ⁶	ERAS associated with lower rates of wound healing disorders, DVT and fever. ERAS group walked greater distances on Day 3. ERAS group spent less time in the	On Day 3, ERAS patients reporting better physical, emotional functioning and less constipation. On Day 7, ERAS patients reported better role, emotional, cognitive and social functioning and less

Study*	Overall study sample size	Baseline PRO sample size	PRO instruments used	Primary endpoint	Treatment outline	Summary of main clinical results	Summary of PRO results/PRO treatment recommendations
Marandola M et al. <i>Minerva Anestesiol.</i> 2005;71,83-91.	62	62	10-point Verbal analogue pain scale	PRO (including QOL or symptoms relief), motor and sensory blockade, discharge time from the recovery room, post-operative side effects	Spinal anesthesia with 10mg of 0.5% hyperbaric bupivacaine versus 1.5ug of sufentanil	Intermediate care unit. ERAS goals met. Less analgesic drugs. Less sedation. Less nausea. Less vomiting. Less urinary retention. Less ileus. Less cognitive and social functioning and less fatigue, dyspnea, insomnia and constipation	10 of 32 sufentanil patients reported moderate to severe pain (3-8 on VAPS) vs 1 of 30 patients in the bupivacaine group
Koga H et al. <i>Int J Urol.</i> 2010;17,759-766.	53	51	EORTC QLQ C-30 Japanese version	Efficacy of induction therapy	Maintenance intravesical BCG Tokyo strain 80mg held over 2 hours given once every 3 months for 1 year versus no maintenance (observation)	Maintenance BCG was associated with lower recurrence rate on univariate but not multivariate analysis	No differences
Ozyuvaci E et al. <i>Urol Int</i> 2005;74,62-67.	50	50	10-point Visual analogue scale for pain	PRO (including QOL or symptoms relief); Blood loss, transfusion requirements, intraoperative complications, quality of analgesia	GA with or without epidural ropivacaine infusion during radical cystectomy. Epidural catheter removed in recovery room.	Higher intraoperative blood loss and more intraoperative blood transfusions for the GA group. Higher PCA demand and delivery in the GA arm. Lower intraoperative mean arterial pressure in the GA plus epidural arm	Higher pain scores in GA arm at all time points: 0, 1, 2, 4, 12 and 24 hours
Johnson MH et al. <i>J Urol.</i> 2013;189, 1268-1274.	50	50	Ad hoc questionnaire (0 to 3-point scale for 5 urinary, and 3 non-urinary symptoms and 3 anticholinergic side-effects)	PRO (including QOL or symptoms relief)	10mg oxybutynin ER versus placebo starting day before and continuing through 6 weekly courses of intravesical BCG	No differences	Increased urinary frequency and burning in treatment group. Fever and flu-like symptoms more common in treatment group. Dry mouth and constipation more common in treatment group