



Health-related quality of life overview after different curative treatment options in muscle-invasive bladder cancer: an umbrella review

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Abstract

Purpose This umbrella review aims to evaluate the quality, summarize and compare the conclusions of systematic reviews investigating the impact of curative treatment options on health-related quality of life (HRQoL) in muscle-invasive bladder cancer (MIBC).

Methods The Cochrane Library, MEDLINE, Embase and Web of Science were searched independently by two authors from inception until 06 January 2020. Systematic reviews and meta-analyses assessing the impact of any curative treatment option on HRQoL in MIBC patients were eligible. Risk of bias was assessed using the AMSTAR 2 tool.

Results Thirty-two reviews were included. Robot-assisted RC with extracorporeal urinary diversion and open RC have similar HRQoL ($n = 10$). Evidence for pelvic organ-sparing RC was too limited ($n = 2$). Patients with a neobladder showed better overall and physical HRQoL outcomes, but worse urinary function in comparison with ileal conduit ($n = 17$). Bladder-preserving radiochemotherapy showed slightly better urinary and sexual but worse gastro-intestinal HRQoL outcomes in comparison with RC patients ($n = 6$). Quality of the reviews was low in more than 50% of the available reviews and most of the studies included in the reviews were nonrandomized studies.

Conclusion This umbrella review gives a comprehensive overview of the available evidence to date.

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Introduction

Bladder cancer (BC) is the 9th most common cancer worldwide with increasing incidence rates in men and people with more advanced age [1]. Thirty per cent of BC patients are diagnosed with muscle-invasive BC (MIBC, stages T2-T4) [2] and up to 45% of patients with non-MIBC (NMIBC)

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will eventually progress to MIBC [3]. Approximately 50% of MIBC patients will develop distant metastases within the first two years after treatment [1] and although mortality rates of BC tend to decrease, 20% of people diagnosed with BC eventually die because of the disease [4].

Patients diagnosed with MIBC are offered different curative treatment options such as neoadjuvant chemotherapy (NAC) followed by radical cystectomy (RC) with extended pelvic lymph node dissection and construction of a new urinary diversion (i.e. ileal conduit, continent reservoir, or neobladder) [1]. However, NAC is still underused in clinical practice [5] and consensus on which type of RC and urinary diversion delivers the best outcomes is still lacking [6].

Minimally invasive surgery such as robotic or laparoscopic RC has gained interest in the last decades as these approaches are considered to reduce morbidity, expedite recovery and decrease length of hospital stay [7, 8]. However, open RC still remains the standard of care [6]. Evidence on which urinary diversion type provides the lowest complication rates also remains unclear. After RC and reconstruction of a urinary diversion, high-risk patients can also be offered adjuvant chemo- and/or radiotherapy [9].

Given the non-neglectable risk of RC associated morbidity which rises up to 30–64% [10], there is growing interest in bladder-preserving alternatives for RC. Trimodality therapy, consisting of maximal transurethral resection of the bladder followed by radiochemotherapy, provides similar oncological outcome as RC in well-selected patients [1, 11].

Treatment decisions are often based on a combination of clinical experience, evidence-based guidelines and patient preferences [12]. Decision-making by MIBC patients is driven by receiving the best care possible and is based on selecting treatment approaches that best fit the patients' lifestyles and personal attributes [13]. Moreover, knowledge about the consequences of treatments on health-related quality of life (HRQoL) has become an important factor in clinical decision-making.

HRQoL refers to the patients' own perceptions of their health and ability to function encompassing physical, psychological, social and spiritual dimensions [14, 15]. Patient-reported outcome measures (PROMS) are questionnaires developed to measure patient-focused outcomes such as HRQoL [16]. A number of cancer (e.g. European Organization for Research and Treatment of Cancer quality-of-life (EORTC QLQ-C30), Functional Assessment of Cancer Therapy-Bladder (FACT-BI)) and bladder cancer-specific (e.g. EORTC QLQ—Bladder Cancer Muscle-Invasive (BLM30), Bladder Cancer Index [BCI]) questionnaires exist to measure different domains of HRQoL [16]. Most of those questionnaires are 30–50 item multiple-choice questionnaires providing a score on scales related to the different HRQoL domains [17].

Several systematic reviews have already compared different treatment options for MIBC patients and evaluated their impact on HRQoL. However, these reviews focus on the same topic with different quality and scope as well as conflicting results. Comparison of those reviews is needed to inform decision-makers on the best available evidence.

This umbrella review aims to evaluate the quality, summarize and compare the conclusions of those systematic reviews investigating the impact of different curative treatment options on HRQoL in patients with MIBC.

Methods

This umbrella review was registered on PROSPERO (CRD42019129524), adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and followed the guidelines provided by the Joanna Briggs Institute [18].

Studies were considered eligible when they met the pre-defined PICO(S)-criteria. The population of interest was nonmetastatic MIBC (i.e. T2-T4 without distant metastases). Interventions could be any curative treatment approach for MIBC (e.g. radiochemotherapy, RC) and the type of comparison depended on the treatment being studied. The outcome of interest was HRQoL, cancer-specific quality of life (QoL) or MIBC-specific QoL (primary or secondary outcome). Only systematic reviews and/or meta-analyses were included. Narrative or scoping reviews were excluded. In addition, abstracts and full texts in any other language than English, French or Dutch were excluded.

Four databases were searched from inception until the search date (06/01/2020): MEDLINE (using the PubMed interface), EMBASE, the Cochrane Library and Web of Science (WoS). Details of the search strategy are available in Appendix 1 (in Supplementary Material). HRQoL, furthermore, cited references of the included reviews and citing references retrieved via WoS were checked.

After removing duplicates, articles were screened by two independent reviewers (ER and TVV) based on title and abstract. Study selection based on full text was performed using the web application Covidence. In case of discrepancies, a third reviewer was consulted (VF). To extract relevant data, a data extraction form was used which was pilot-tested with three studies. Data extraction was performed independently by two reviewers (ER & TVV). In case of disagreements, a third reviewer was consulted (VF).

Risk of bias of the included reviews was assessed by one person (LVW) using the Assessing the Methodological quality of Systematic Reviews (AMSTAR 2) tool [19]. The AMSTAR 2 tool contains fourteen items for systematic reviews and two additional items for meta-analyses.

A narrative synthesis was conducted to describe key characteristics and summarize the findings of the included reviews. The results were compared and reported per treatment approach.

Results

The systematic search yielded 7,698 articles of which 32 reviews were eligible. The PRISMA diagram of the review selection is shown in Fig. 1, including reasons for full-text exclusion.

Of the 32 included reviews, 19 reviews investigated the impact of RC and different urinary diversion types on HRQoL [20–34]. Two reviews examined female sexual functioning after pelvic organ-preserving RC [35, 36]. Differences between RARC and ORC were searched in ten reviews [37–46] and six reviews assessed bladder-preserving radiochemotherapy [20, 21, 47–50]. One review summarized the evidence regarding medical oncological treatments before, during or after other treatment modalities [50]. Details about the characteristics of the included reviews are shown in Table 1.

The quality assessment showed an overall poor quality of the included reviews. Only 13 reviews had a score of half or more on the AMSTAR 2 tool [29, 32–34, 36, 40, 42, 44–46, 50–52]. Higher quality was seen in reviews that also conducted a meta-analysis and in recent systematic reviews. A summary of the quality assessment is shown in Table 2.

The results are presented separately for each treatment approach. An overview of the conclusions of each review is presented in Table 3.

Urinary diversion: ileal conduit, continent diversion, and orthotopic neobladder

Several reviews reported well maintained or only a slightly decrease in overall HRQoL, whereas problems with urinary and sexual functioning were common after all urinary diversion types [20, 22, 53, 54]. One review synthesized both qualitative and quantitative evidence and identified also other important HRQoL domains related to bowel functioning, body image, sleep, social functioning and support from family, friends and the healthcare team [27]. A review of females undergoing RC showed worse emotional—and role functioning, fatigue and appetite in comparison with the general population [34]. Two reviews mentioned that HRQoL improved until one year after surgery and then remained stable [23, 51].

Six of the 17 reviews (none of them were meta-analysis) found no differences in HRQoL between the different urinary diversion types. One meta-analysis found no difference in overall HRQoL, but reported a small benefit for ileal

conduit patients in physical health, which was attributed to poorer urinary and sexual functioning in neobladder patients [54]. Also, another meta-analysis found better urinary function in ileal conduit patients [52].

Contradictory, six of the 17 reviews (of which three were meta-analyses) stated that HRQoL was significantly better in patients receiving a neobladder compared to ileal conduit patients. Benefits for neobladder patients were reported for overall HRQoL, physical functioning, sexual functioning, social functioning and self-image. However, age, gender, type of questionnaires and follow-up time were important factors when interpreting the results. Furthermore, one of the meta-analyses reporting better overall HRQoL in neobladder patients found better urinary function in ileal conduit patients, which was particularly contributed to the burden of nocturnal incontinence in neobladder patients [51].

Pelvic organ-preserving RC versus standard RC

Two reviews concluded that pelvic organ-preserving RC is safe and could potentially lead to better preserving female sexual function compared to conventional RC. However, strong conclusions about which surgery technique is preferred based on HRQoL outcomes could not be made due to the limited studies available [35, 36].

Open versus robot-assisted RC

Ten reviews were included comparing HRQoL outcomes between RARC with extracorporeal urinary diversion and ORC. Three reviews did not give an overall conclusion about HRQoL [37–39]. The seven most recent reviews concluded that there were no HRQoL differences between RARC and ORC [40–46]. No reviews included studies on RARC with intracorporeal urinary diversion.

Bladder-preserving radiochemotherapy

The most reported HRQoL issues in MIBC patients following radiation therapy were bowel problems. Defecation urgency seemed to be most distressing, while diarrhoea/loose stool and faecal incontinence (20%) were more common [27]. Other HRQoL issues reported after radiation therapy were urinary frequency, sexual problems, fatigue and malaise [27].

Five reviews compared bladder-preserving strategies with RC. Three reviews described better HRQoL outcomes after bladder-preserving strategies in comparison with RC. Botteman et al. concluded that bladder-preserving strategies have better short-term HRQoL in the physical, psychological and sexual domains. However, these differences disappeared after 18 months [20]. Although based on low-quality studies, Taarnhoj et al. suggested that

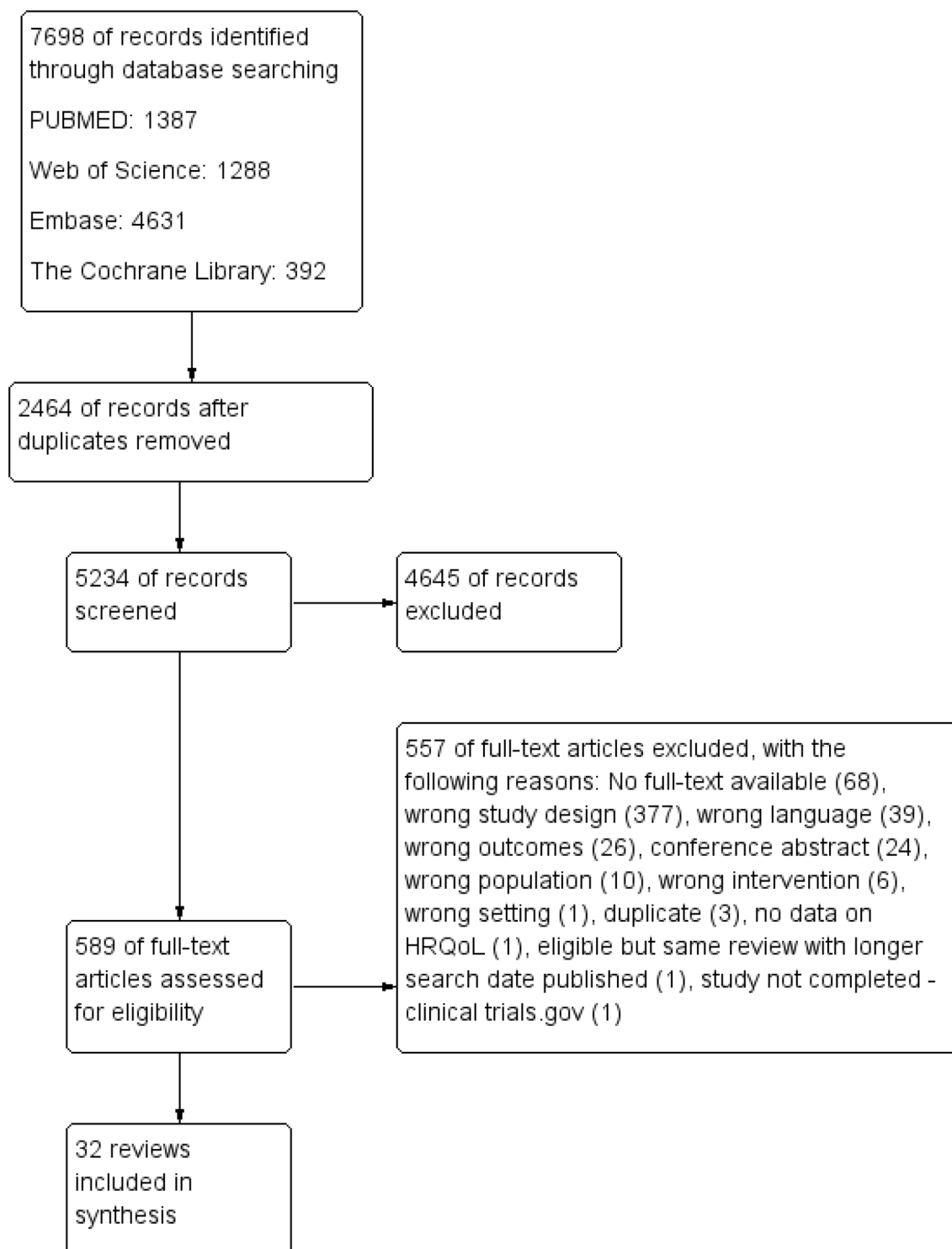


Fig. 1 PRISMA diagram

bladder, bowel and/or sexual function were superior to that of cystectomy treated individuals [50]. Feuerstein et al. concluded that MIBC patients receiving radiation therapy showed similar or better general HRQoL, satisfactory

urinary and sexual domains, but worse gastro-intestinal symptoms compared to RC. The other reviews did not make conclusions regarding HRQoL outcomes. However, the two studies described in the review of Ploussard et al.

Table 1 Characteristics of the included reviews

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Urinary diversion: ileal conduit, continent diversion and orthotopic neobladder								
Botteman, M.F. [20]	To review the international medical literature To better understand the impact of bladder cancer on patient HRQL	7 online databases 4 grey literature	11	1996–2001	NC	8 CS, 1 Prosp, 1 RCT, 1 RS	878	Author designed (3), IIEF (1), Interview (1), SF-36 (3), POMS (1), validated emotional instrument and sexual function (1), Modified EORTC (1), SIP (2), MCT (1), Not specified (1), AUA symptom index and associated HRQoL items (1)
Parkinson, J. P. [21]	To review the current data regarding the impact of various therapeutic alternatives for bladder cancer on health-related (HR) quality of life (QOL)	1 Medline	21	NR	NC	NR	1704	Modified Munich Life Dimension List (1), Nonvalidated questionnaire (13), EORTC-QLQ-C30 (1), Modified EORTC-QLQ-C30 (2), NHP (1), SF-36 (6), Brief Index of Sexual Functioning for Women (1), Modified radiation treatment questionnaire (1) Validated indigenous questionnaire (1), Symptom Checklist-90-Revised (1), Quality of Life Scale (1), SIP (2), Life Satisfaction Questionnaire (1), FACT-G (1), FACT-BL (1), HADS (1), Not reported (7)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Gerhartz, E. W. [22]	To critically examine the evidence supporting the widely accepted notion that patients undergoing continent urinary tract reconstruction after cystectomy experience superior quality of life outcomes than patients receiving a conduit	1 Medline	36	NR	NC	4 Prosp, 32 RS/CS	NC	Interview (7), Self-designed questionnaire (22), BDI (1), POMS (2), SF-36 (6), EORTC QLQ-C30 (2), FACT-G (1), FACT-BL (1), SIP (2), HADS (1), MCT (1), VAS (1)
Porter, M. P. [23]	To investigate the premise that continent forms of urinary diversion offer superior HRQoL	1 Medline	15	1987–2002	SR	14 CS/RS, 1 Prosp	1674	Ad hoc questionnaire/instrument (10), BDI (1), PMS (2), SF-36 (6), FACT-G (1), Fragen zur Lebenszufriedenheit Module (1), Sexual history form (1), Body image scale (1), QOL questionnaire (1), EORTC-QLQ-30C (2), FACT-BL (1), HADS (1)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Somani, B. K. [54]	To assess the evidence base that underpins each of the major forms of transposed intestinal segment surgery (ileal conduit diversion, continent urinary diversion, and orthotopic bladder replacement) and to explore the meaning, determinants, and measurements of QoL	4 Medline Embase Cinahl Cochrane	46	1980–2010	SR	8 Prosp, 38 RS/CS	4186	Self-designed questionnaire (17), BDI (2), POMS (1), Physical impact (1), Interview (7), SIP (2), MCT (2), Urinary symptoms (1), Activity level (1), Overall well-being (1), VAS (1), Self-reporting questionnaire (4), EORTC QLQ-C30 (7), SF-36 (9), FLZM (1), FACT-G (1), FACT-BL (6), HADS (2), BCI (2), Patient satisfaction (1), EORTC QLQ- BLM30 (1), SEIQoL-DW (1), BIS (1)
Kassouf, W. [25]	To review the literature regarding indications, postoperative care, complications, quality of life measures, as well as functional and oncological outcomes that have been published on patients with OBS	1 Medline	NR	NR	NC	NR	NR	NR

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Hautmann, R. E. [26]	To review the literature regarding indications, surgical details, postoperative care, complications, functional outcomes, as well as quality of life measures with different forms of urinary diversion (UD)	NR	NR	NR	NC	NR	NR	NR
Pertis, N. [27, 47]	To develop a conceptual framework organizing the most important components of global HRQoL in BCa. This framework will permit better understanding of the experiences of all BCa patients and serve as the foundation for the development of a novel BCa-specific utility instrument	4 MEDLINE, Cinahl, Embase, PsychInfo	170	NR	No	18 qualitative, remainder cohort studies	NR	NR
Ali, A. S. [28]	To investigate which of the available forms of urinary diversion offers a superior QoL after cystecTomy	4 Medline, CINAHL, Embase, Cochrane	21	1997–2012	SR	4 Prosp, 17 CS/RS	2069	SF-36 (6), EORTC QLQ-C30 (8), Sickness Impact Profile (SIP) (2), FACT-BL (3), BCI (2), SEIQoL (1), Self-designated Q (3), FACT-G (1), MCT (1), HADS (1), Patient satisfaction Q (1), BDI (1), BIS (1), EORTC QLQ-BLM30 (1)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Cerruto, M. A. [29]	To update the review of all relevant published studies on the comparison between ONB and IC using validated HRQoL questionnaires	3 Medline Embase CINAHL	22	1997–2004	SR and meta (18 studies)	4 Prosp 18 RS	1788	SIP (1), MCT (1), EORTC QLQ-C30 (10), SF-36 (6), BDI (1), FACT-G (1), FACT-BL (3), BCI (2), EORTC QLQ-BLM30 (3), SEIQoL (1), FACT-VCI(1) EORTC QLQ-C30 (3), SF-36 (1), FACT-BL (1), BCI (2), Body image scale (1), erectile function and desire score, bladder cancer subscale questionnaire, and proportion of continent patients
Crozier, J. [30]	To identify differences in patient selection, operative parameters, complications and quality of life outcomes in ileal conduit and neobladder	1 Medline	10	NR	SR	NR	4941	EORTC QLQ-C30 (3), SF-36 (1), FACT-BL (1), BCI (2), Body image scale (1), erectile function and desire score, bladder cancer subscale questionnaire, and proportion of continent patients
Ghosh, A. [31]	To elucidate whether the current literature indicates that orthotopic neobladder provides better QoL outcomes post-tectomy than other methods of urinary diversion	6 Medline Embase Scopus CINAHL Cochrane PsycINFO	22	1998–2014	SR	5 Prosp 17 CS/RS	2450	EORTC QLQ-C30 (4), FACT-VCI (1), SEIQoL (1), BCI (1), SF-36 (1), SIP (1), EORTC-BIS (1), Continence Q (1), Not specified (4)
Yang, L. S. [32, 54]	To compare QOL differences between continent and incontinent urinary diversion and provide a guide for the likely QOL outcomes compared To baseline and reference populations	2 MEDLINE EMBASE	20	2000–2014	SR and meta	9 Prosp, 19 RS, 1 case series	3754	IIEF (1), FACT-BL (7), SF-12 (1), WHO-QOL-BREF (1), QLQ-C30 (8), QLQ-BLM30 (2), SF-36 (10), FACT-VCI (1), BDI (2), FACT-G (5), ICSmaleSF (1), IIEF-5 (1), VAS (1), BCI (2), BID (1), KPS (1), Study's own questionnaire (5), HADS (2), IPSS (1), SIP (1), MOS (1)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Cerruto, M. A. [33]	To review of all relevant published studies on the comparison between IONB and IC using validated HRQoL questionnaires	3 Medline Embase CINAHL	10	2000–2013	SR and Meta	10 RS	691	SF-36 (4), EORTC QOL-C30 (4), FACT-G (1), FACT-BL (2), EORTC QOL-BLM30 (2), FACT-VCI (1)
Smith, A. B. [34]	To better characterize female-specific functional outcomes following RC & to integrate the available evidence regarding female-specific functional outcomes following RC for BCa, provide an overview of functional outcomes in the female RC/BCa population, and identify potential areas for future research	2 Medline Embase	9	NR	SR	NR	NR ^o	Nonstandardized questionnaire, BSI-18, FACT-VCI, SF-36, EORTC QLQ-30, EORTC QLQ-BLM30, FACT-BL
Shi, H. [51]	To perform a meta-analysis to compare post-ICD and post-ONB HRQoL in patients with BC	3 Medline Embase Cochrane + 3 grey literature resources	26	1987–2012	SR and meta	5 Prosp, 21 CS/RS	2507	EORTC QLQ-C30 (9), EORTC QLQ-BLM30 (3), EORTC-BIS (2), Self-designed (5), SF-36 (7), Interview (2), FACT-G (2), FACT-BL (2), FACT-VCI (4), BCI (5), SIP (1) BCI (4)
Ziouiou, I. [52]	To compare HRQoL, assessed with the BCI questionnaire, in patients undergoing ONB and IC after RC	3 PubMed ScienceDirect Cochrane + clinicaltrials.gov	4	2010–2016	SR and meta	1 Prosp, 3 RS	528	

Pelvic organ-preserving radical cystectomy and urinary diversion

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Zahran, M. H. [35]	To provide a comprehensive overview of the impact of radical cystectomy and urinary diversion on women's sexual life, and sequentially HRQoL, affecting factors and modalities of assessment	2 Medline Wiley Online Library	11	1985–2015	SR, NC	3 Prosp, 8 RC/CS	361 ^o	FSFI (5), Modified 10-item version of the FSFI questionnaire (1), Nonvalidated self-designed questionnaire (5)
Veskima, E. [36]	To compare pelvic organ-preserving RC (POPRC) with standard RC in women who undergo curative surgery for bladder cancer, in terms of sexual, oncological, and urinary function outcomes	3 Medline Embase Cochrane + clinicaltrials.gov	7	NR	SR	4 Pros, 11 RS	167 ^o	Interview (3), FSFI (3), Contilife (1)
Robot-assisted and open radical cystectomy								
Orvieto, M. A. [37]	To review the current experience and status of RARC worldwide and compares the available published data with the gold standard ORC series	1 Medline	2	NR	Critical review, NC	1 Prosp 1 NR	350	NR
Al-Tartir T. [38]	To understand the comparative effectiveness of RARC at operative, functional and oncologic outcomes before considering it as a new standard	NR	4	2009–2014	SR	1 RCT, 3 cohort studies	NR	FACT-YCI (1), BCI (1), NR (2)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Wilson, T. G. [39]	To systematically review existing peer-reviewed literature on robot-assisted RC (RARC), extended lymphadenectomy, and urinary reconstruction	3 Medline Scopus WoS	1	2014	SR	RS	182	NR
Tan, W. S. [40]	To compare RARC versus ORC on perioperative and histopathological outcomes. Secondary outcomes include quality of life assessment, oncological outcomes and cost analysis	3 Medline Embase Wos + clinicaltrials.gov	3	2010–2015	SR (and meta – not for qol)	NR	NR	FACT-VCI (1), EORTC QLQ-C30 (2), FACT-G (1), FACT-BL(1) Trial Outcome Index questionnaire (1)
Attalla, K. [41]	To critically review the literature comparing ORC with RARC	3 PubMed, Wos, Scopus	3	2013–2016	SR, NC	2 RCT, 1 RS	NR	FACT-VCI (1), EORTC QLQ-C30 (1), BCI (1)
Lauridsen, S. V. [42]	To evaluate the effect of RARC compared to open RC on complications and secondary on length of stay, time back to work, and HRQoL	4 PubMed Cochrane Embase CINAHL	3	2014–2016	SR and meta	RCTs	239 (voor 4 studies)	FACT-BL (1), FACT-G (1), FACT-VCI (1), EORTC QLQ-C30 (1)
Lobo, N. [43]	To investigate whether a totally intracorporeally radical cystectomy can be considered the new 'gold standard' in BC	3 Medline ISI Web of Knowledge Cochrane	3	2014–2015	SR	NR	NR	FACT-VCI (1), EORTC QLQ-C30 (1), BCI (1)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Kimura, S. [45]	To assess the differential perioperative complications and HRQoL outcomes between RARC and ORC	4 Medline Scopus WoS The Cochrane library ORC	6	2014–2018	SR and meta	3 RCT, 1 Prosp, 1 CS	1073	FACT-YVCI (2), BCI (3), EORTC QLQ-C30 (1), BIS (1)
Rai, B. P. [44]	To assess the effects of robotic-assisted radical cystectomy versus open radical cystectomy in adults with bladder cancer	9 The Cochrane library Medline Embase WoS Cancer Research UK Institute of cancer research Clinicaltrials.gov BioMed Central ISRCTN registry World Health Organization International Clinical Trials Registry Platform	4	2015–2018	SR and meta	RCTs	270	FACT-BL (1), FACT-YVCI (2), EORTC QLQ-C30 (1)
Sathianathan, N. J. [46]	To assess the benefits and harms of RARC compared to ORC in patients with BC	6 Medline Embase ScienceDirect The Cochrane Library The HTA database Web of Science	3	2013–2018	SR and meta	RCTs	271	NR
Bladder-preserving radiochemotherapy Botteman, M.F. [20]	To review the international medical literature To better understand the impact of bladder cancer on patient HRQL	7 online databases 4 grey literature	5	1988–2000	NC	1 CS, 1 RCT, 2 Prosp/RS	256	Author designed (3), IIEF (1), Interview (1), SF-36 (3), POMS (1), validated emotional instrument and sexual function (1), Modified EORTC (1), SIP (2), MCT (1), Not specified (1), AUA symptom index and associated HRQoL items (1)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Parkinson, J. P. [21]	To review the current data regarding the impact of various therapeutic alternatives for bladder cancer on health-related (HR) quality of life (QOL)	1 Medline	21 3RT	NR	NC	NR	1704	Modified Munich Life Dimension List (1), Nonvalidated questionnaire (13), EORTC-QLQ-C30 (1), Modified EORTC-QLQ-C30 (2), Nottingham Health Profile (NHP) (1), SF-36 (6), Brief Index of Sexual Functioning for Women (1), Modified radiation treatment questionnaire (1) Validated indigenous questionnaire (1), Symptom Checklist-90-Revised (1), Quality of Life Scale (1), SIP (2), Life Satisfaction Questionnaire (1), FACT-general (1), FACT-bladder specific (1), HADS (1), Not reported (7)
Pertlis, N. [27, 47]	To develop a conceptual framework organizing the most important components of global HRQOL in BCa. This framework will permit better understanding of the experiences of all BCa patients and serve as the foundation for the development of a novel BCa-specific utility instrument	4 MEDLINE, Cinahl, Embase, PsychInfo	170	NR	SR	18 qualitative, remainder cohort studies	NR	NR

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Ploussard, G. [48]	To assess the modern bladder preservation treatment modalities, focusing on TMT in MIBC	2 -PubMed -Cochrane	2	1996–2002	SR	1 RS, 1 CS	NR	NR
Feuerstein, M. A. [49]	To review patient-reported outcomes for bladder preservation treatment with a focus on patients eligible for radical cystectomy, for whom a comparison of patient-reported outcomes is most relevant	1 MEDLINE	6	1996–2011	NC	2 Prosp 4 RS	278	FACT-G (1), FACT-BL (1), EORTC QLQ-C30 and five ad hoc bladder function question (1), Validated questionnaire modified from EORTC QLQ-C30 (1), Ad hoc questionnaire on libido, frequency of sexual activity and sexual function (1), Ad hoc questionnaire on urinary, bowel and sexual function, psychological symptoms and global well-being (1), Trade-off question of acceptable shortened survival for excluding radiotherapy (1), SF-36 (1), Ad hoc questionnaires modified from prostate and rectal radiotherapy (1), Brief Index of Sexual Functioning for Women (1)

Table 1 (continued)

First author, year	Objective(s)	# Sources	# HRQoL studies SR*	Date range included studies	Type of review	Study designs	# Patients	HRQoL measures
Taarnhoj, G. A. [50]	To assess the existing literature on QoL in patients with MIBC undergoing medical oncological treatment	2 PubMed Embase	6	2002–2017	SR	NR	798	EORTC QLQ-C30 (2), EORTC QLQ-BLM30 (2), Nonvalidated/self-made (2), SF-36 (2), FACT-G (1), FACT-BL (1), IPSS (1), EPIC (2), EQ-5D-5L (1), IOCV2 (1)

WoS Web of Science; *HRQoL* Health-related quality of life; *NC* not clear; *CS* cross-sectional; *Prosp* prospective; *RCT* randomized controlled trial; *RS* retrospective; *HRQoL* measures: *IEF* International Index of Erectile Function; *SF-36*, Short Form Health Survey -36 items; *POMS* Profile of Mood States; *EORTC* European Organization for Research and Treatment of Cancer; *Quality of Life Questionnaire-Core 30 (QLQ-C30)*; *SIP* Sick Impact Profile; *MCT* Meta-Contrast Test; *AUA* American Urological Association; *NHP* Nottingham Health Profile; *FACT-G* Functional Assessment of Cancer Therapy-general; *FACT-BL* Functional Assessment of Cancer Therapy- Bladder Specific; *FACT-VCI* Functional Assessment of Cancer Therapy- Vanderbilt Cystectomy Index; *HADS* Hospital and Depression scale; *BDI* Beck Depression Inventory; *VAS*, Visual Analogue Scale; *PMS*, Premenstrual Syndrome; *FLZM* Fragen zur Lebenszufriedenheit; *SEIQoL-DW* Schedule for the Evaluation of the Individual Quality of Life-Direct Weightings; *KPS* Karnofsky Performance Score; *IPSS* International Prostate Symptom Score; *MOS* Medical Outcome Study; *BSI* Brief Symptom Inventory; *FSFI* Female Sexual Function Index; *EPIC* Expanded Prostate Cancer Index Composite; *EQ-5D-5L* euroQoL 5-dimension 5-level; *IOCV2* Impact of Cancer version 2

*If reviews assessed several outcomes, then only the studies reporting on HRQoL were taken into account

⁹Only females with BC are included

Table 2 AMSTAR assessment

	Did the research questions and inclusion criteria include PICO?	Did the review worked with a written protocol with independent verification?	Is the selection of the study designs for inclusion in the review explained?	Did the review authors use a comprehensive literature search strategy?	Did the review authors perform study selection in duplicate?	Did the review authors perform data extraction in duplicate?	Did the authors provide a list of excluded studies and justify the exclusions?	Did the review authors describe the included studies in adequate detail?	Did the authors use a satisfactory technique for assessing the risk of bias?	Did the authors report on the sources of funding for the studies included?	If meta-analysis, did the authors use appropriate methods?	If meta-analysis, did the authors assess the potential impact of RoB?	Did the authors account for RoB when interpreting/discussing the results?	Did the authors provide an explanation for any heterogeneity observed?	Did the authors carry out an adequate investigation of publication bias?	Did the authors report conflict of interest, including any funding?
Ali, 2015	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✗	✗	✗	✔
Attalla, 2017	✔	✗	✔	✗	✗	✗	✗	✔	✗	✗	n.a.	n.a.	✗	✔	✗	✔
Botteman, 2003	✔	✗	✗	✗	✔	✗	✗	✔	✗	✗	n.a.	n.a.	✗	✗	✗	✗
Cerruto, 2015	✔	✗	✔	✗	✔	✔	✗	✔	✗	✗	✔	✔	✔	✔	✔	✔
Cerruto., 2017	✔	✗	✔	✗	✔	✔	✔	✔	✗	✗	✔	✔	✗	✔	✔	✗
Crozier, 2016	✔	✗	✗	✗	✗	✗	✔	✔	✗	✗	n.a.	n.a.	✔	✔	✗	✔
Feuerstein, 2015	✔	✗	✔	✗	✗	✗	✗	✔	✗	✗	n.a.	n.a.	✗	✔	✗	✔
Gerharz, 2005	✗	✗	✔	✗	✗	✗	✗	✔	✗	✗	n.a.	n.a.	✔	✔	✗	✗
Ghosh, 2016	✔	✗	✗	✗	✗	✗	✔	✗	✗	✗	n.a.	n.a.	✔	✗	✗	✔
Hautmann, 2013	✗	✗	✔	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✔	✔	✗	✔
Kassouf, 2010	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✔	✗	✗	✔
Kimura, 2019	✔	✔	✔	✔	✔	✔	✔	✔	✔	✗	✔	✗	✔	✔	✗	✔
Lauridsen, 2017	✔	✔	✔	✔	✔	✔	✔	✔	✔	✗	✔	✔	✔	✗	✗	✔
Lobo, 2018	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✗	✗	✗	✔
Oderda, 2008	✗	✗	✗	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✗	✗	✗	✔
Orvieta, 2011	✗	✗	✗	✗	✗	✗	✗	✔	✗	✗	n.a.	n.a.	✔	✗	✗	✗
Parkinson, 2004	✔	✗	✗	✗	✗	✗	✗	✔	✗	✗	n.a.	n.a.	✔	✔	✗	✗
Perlis, 2014	✗	✗	✗	✔	✔	✗	✗	✗	✗	✗	n.a.	n.a.	✗	✗	✗	✗

Table 2 (continued)

	Did the research questions and inclusion criteria include PICO?	Did the review worked with a written protocol with independent verification?	Is the selection of the study designs for inclusion in the review explained?	Did the review authors use a comprehensive literature search strategy?	Did the review authors perform study selection in duplicate?	Did the review authors perform data extraction in duplicate?	Did the authors provide a list of excluded studies and justify the exclusions?	Did the review authors describe the included studies in adequate detail?	Did the authors use a satisfactory technique for assessing the risk of bias?	Did the authors report on the sources of funding for the studies included?	If meta-analysis, did the authors use appropriate methods?	If meta-analysis, did the authors assess the potential impact of RoB?	Did the authors account for RoB when interpreting/discussing the results?	Did the authors provide an explanation for any heterogeneity observed?	Did the authors carry out an adequate investigation of publication bias?	Did the authors report conflict of interest, including any funding?
Ploussard, 2014	✓	✗	✓	✗	✗	✗	✓	✓	✗	✗	n.a.	n.a.	✓	✗	✗	✓
Porter, 2005	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	n.a.	n.a.	✓	✗	✗	✓
Rai, 2019	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✗	✓	✓	✗	✓
Sathianathen, 2019	✓	✓	✗	✓	✓	✓	✗	✗	✓	✗	✓	✗	✓	✓	✗	✓
Shi, 2018	✓	✗	✓	✓	✗	✗	✗	✓	✗	✗	✓	✗	✓	✓	✓	✓
Smith, 2016	✓	✗	✓	✗	✓	✗	✓	✗	✗	✗	n.a.	n.a.	✓	✓	✗	✓
Somani, 2010	✗	✗	✓	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✓	✓	✗	✓
Taarnhøy, 2019	✓	✗	✗	✓	✗	✗	✓	✓	✗	✗	n.a.	n.a.	✓	✓	✓	✓
Tan, 2016	✓	✗	✓	✓	✓	✗	✓	✓	✗	✗	✓	✗	✓	✓	✗	✓
Veskimäe, 2017	✓	✓	✓	✓	✓	✗	✓	✓	✗	✗	n.a.	n.a.	✓	✓	✗	✓
Wilson, 2015	✓	✗	✗	✗	✗	✗	✗	✗	✗	✗	n.a.	n.a.	✓	✗	✗	✓
Yang, 2016	✓	✗	✓	✗	✓	✓	✗	✓	✗	✗	✓	✓	✓	✓	✓	✓
Zahran, 2016	✗	✗	✗	✗	✗	✗	✗	✓	✗	✗	n.a.	n.a.	✗	✓	✗	✓
Ziouziou, 2018	✓	✗	✗	✗	✓	✗	✓	✓	✗	✗	✓	✗	✓	✓	✓	✓

reported better urinary and sexual HRQoL outcomes in comparison with RC.

Neoadjuvant chemotherapy

One recent review assessed the impact of medical oncological treatment on HRQoL in MIBC patients. Although they intended to report on studies evaluating NAC, they found no studies evaluating HRQoL during NAC. Other medical

oncological treatments were in the palliative or in the non-MIBC setting, which were not part of this review [50].

Discussion

This umbrella review summarized the results and evaluated the quality of systematic reviews evaluating the impact of curative treatment approaches on HRQoL in patients with

Table 3 Conclusions of the included reviews

First author	Year	# Studies	Key conclusion on HRQoL	Quality rating /16
Urinary diversion: ileal conduit, continent diversion and orthotopic neobladder				
Botteman, M	2003	35	Collectively, the findings of these studies suggest that overall HRQL decreases with use of diversion, but not severely, and that decreased HRQL occurs principally in the sexual and urinary domains. Although most authors originally had hypothesized that continent reservoir techniques (such as cutaneous or neobladder) should result in better HRQL compared with the conventional incontinent ileal conduit, available data do not seem to conclusively support any difference between groups. Attribution of better or worse HRQL to specific diversion procedures remains unresolved	3
Parkinson, J. P	2004	26	In patients undergoing cystectomy, data related to urinary diversion do not show a conclusive advantage for one diversion type over another. There is a lack of data comparing conservative and invasive therapies for bladder cancer at this time	4
Gerharz, E. W	2005	36	Most studies show that overall quality of life after cystectomy remains good in most patients with expected problems with urinary diversion and sexual dysfunction. Within the existing literature, few differences have been demonstrated between diversion groups, suggesting that patients adapt to whatever is required of them. The existing literature does thus not support the assumption that continent reconstruction provides better quality of life than ileal conduit diversion	4
Porter, M. P	2005	15	No conclusion can be drawn about which diversion offers the best HRQOL	4
Somani, B. K	2010	46	Although the reports suggest a reasonably well-maintained QoL after all transposed intestinal segment surgical options, most were retrospective studies, and the few prospective nonrandomized studies had limitations. From the available published evidence, it still remains unclear if one form of transposed intestinal segment surgery is superior to another in terms of QoL	4
Kassouf, W	2010	NR	No specific conclusion for HRQoL	2
Hautmann, R. E	2013	NR	No specific conclusion for HRQoL	4
Perlis, N	2014	NR	No specific conclusion for HRQoL	2
Ali, A. S	2015	21	Orthotopic neobladder urinary diversion shows a marginally better quality of life scores compared to ileal conduit diversion especially when considering younger and fitter patients	1
Cerruto, M. A	2015	22	Significant advantage of IONB compared to IC in terms of HRQoL but due to heterogeneity in several aspects, randomized controlled trials comparing different types of UD using validated, disease-specific HRQoL tools are needed	11
Crozier, J	2016	10	These findings suggest slightly better quality of life in the neobladder group	6
Ghosh, A	2016	22	This review highlights that recent trends suggest that neobladder provides better QoL outcomes than its comparators	4
Yang, L. S	2016	29 20 QoL	QOL is comparable between continent and incontinent urinary diversions, though physical health may benefit more from ileal conduit. Urinary and sexual functions remain suboptimal compared to reference populations for both methods	12
Cerruto, M. A	2017	10	Significant advantage of the IONB subgroups but due to heterogeneity in several aspects, randomized controlled trials comparing different types of UD using validated, disease-specific HRQoL tools are needed	10
Smith, A. B	2017	9	QOL was studied as a comparison between diversion types and the general population. Although there were few differences in HRQOL between diversion types, significant differences in emotional problems, role functioning, fatigue, and appetite were noted among women undergoing RC compared with controls of the general population	7
Shi, H	2018	26	ONB patients are more likely to have a better global health status than ICD patients. However, ONB patients are more likely to experience urinary function problems that influence their quality of life. Regardless of the type of urinary diversion surgery, the gradual improvement in HRQoL over the preoperative status tended to stabilize after 12 months postoperatively	8
Ziouziou, I	2018	4	Better HRQoL in urinary outcomes in IC patients compared with ONB patients. No conclusion can be made regarding the sexual outcomes because of age differences between the IC and ONB patients	9

Table 3 (continued)

First author	Year	# Studies	Key conclusion on HRQoL	Quality rating /16
Pelvic organ-preserving radical cystectomy and urinary diversion				
Zahran, M. H	2016	11	Genital sparing and nerve-sparing cystectomy seem to be effective in the preservation of female sexual function compared to conventional cystectomy; however, well-designed, prospective, randomized studies are needed to prove this	3
Veskimaie, E	2017	15 7 QoL	For well-selected patients, sparing female reproductive organs during RC appears to be oncologically safe and provides improved functional outcomes. The overall quality of the evidence was low as the included studies were underpowered with a significant RoB and confounding. For the same reason it is also difficult to define a preserving technique that performs better than others	11
Robot-assisted and open radical cystectomy				
Orvieto, M. A	2011	1	No specific conclusion for HRQoL	2
Al-Tartir T	2015	4	No specific conclusion for HRQoL	
Wilson, T. G	2015	1	No specific conclusion for HRQoL	3
Tan, W. S	2016	3	All studies concluded that there was no difference in QoL between the RARC and ORC groups	10
Attalla, K	2017	3	Prospective and retrospective data suggest oncologic outcomes, longterm complications, and HRQoL to be similar between RARC and ORC	5
Lauridsen, S. V	2017	3 qol	This review presents evidence for RARC not being superior to ORC regarding complications, LOS and HRQoL	14
Lobo, N	2018	3 qol	The studies show equivalence between RARC and ORC for HRQoL outcomes	1
Kimura, S	2019	3 qol	No difference between RARC and ORC in HRQoL	13
Rai, B. P	2019	3qol	RARC and ORC may have similar outcomes with regard to quality of life	14
Sathianathen, N. J	2019	3 qol	RARC and ORC are largely comparable in terms of quality of life outcomes	10
Bladder-preserving radiochemotherapy				
Botteman, M	2003	5	Overall, bladder-preserving strategies seem to offer short-term HRQL benefit in the physical, psychological, and sexual domains	3
Parkinson, J. P	2004	3 RT	There is a lack of data comparing conservative and invasive therapies for bladder cancer at this time	4
Perlis, N	2014	NR	Most common side effects of radiotherapy are bowel problems. Other issues are urinary and sexual dysfunctioning, fatigue and malaise. No comparison with RC was made	2
Ploussard, G	2014	2	A growing body of accumulated data suggests that TMT leads to acceptable outcomes and may therefore be considered a reasonable treatment option in well-selected patients. TMT can be discussed not only in patients unfit for surgery but also for those patients who have MIBC and are not willing to undergo surgery. No specific conclusion for HRQoL outcomes	6
Feuerstein, M. A	2015	6	Bladder preservation with radiotherapy appears to offer a similar or better general quality of life with satisfactory sexual and urinary function but detrimental gastro-intestinal effects compared to radical cystectomy. It is unclear whether these data can be applied to typical bladder cancer patients because of the small sample sizes, eligibility criteria, and single-institution studies	5
Taarnhoj, G. A	2019	21 6 chemoRT	For the patients having undergone RT as a bladder conserving strategy, the majority of the studies found the patients to have good or satisfactory bladder, bowel, and/or sexual function and superior to that of cystectomy treated individuals when these were used as control groups	9

MIBC. Based on the available evidence, no conclusions can be drawn for NAC, RARC versus ORC, and pelvic organ-sparing RC in female patients. The most recent reviews showed better overall and physical HRQoL outcomes in patients with a neobladder in comparison with ileal conduit patients. Ileal conduit patients showed better urinary function in comparison with neobladder patients. The evidence

regarding bladder-preserving radiochemotherapy showed slightly better HRQoL outcomes in patients receiving RT in comparison with RC patients, especially in urinary and sexual domains. Bowel problems were the most commonly reported problems in RT patients.

Although no evidence exist on the superiority of RARC over ORC in terms of HRQoL, this can only be postulated for

RARC with extracorporeal urinary diversion as no study in the included reviews used intracorporeal diversion. Urinary diversion reconstruction accounts for the majority of complications following radical cystectomy. The requirement for a mini-laparotomy for the extracorporeal urinary diversion reconstruction has been postulated to negate potential perioperative benefits of a minimally invasive approach [55]. With intracorporeal urinary diversion gaining popularity and experience, future studies should compare ORC versus RARC with intracorporeal diversion.

It is also important that future studies incorporate a prospective design with appropriate time-points and measurements of HRQoL. This is important because RARC is considered to accelerate postoperative recovery while prospective studies are still choosing month 3 post-surgery as first time-point to measure HRQoL [43], which creates an unknown ‘blackbox’ between surgery and month 3. A promising study is on its way that compares ORC versus RARC with intracorporeal urinary diversion and evaluates PROs at week 5 and also uses activity trackers to compare functional recovery after RARC versus ORC [56].

The most evaluated treatment approach was the construction of a new urinary diversion. Although overall and physical HRQoL seemed to be better in neobladder patients, this finding might only be true for a subgroup of patients. The current literature is solely based on nonrandomized studies which might induce selection bias (e.g. younger and fitter patients in the neobladder groups).

Time of conduction of the reviews seemed to be most important when interpreting the results. Treatment approaches and surgical techniques may have changed over time, which in turn may affect postoperative HRQoL [57]. Neobladder and ileal conduit were considered inferior in the older systematic reviews, while the more recent reviews concluded that neobladder patients have better HRQoL outcomes compared to ileal conduit patients.

The evidence related to bladder-preserving radiochemotherapy showed slightly better urinary and sexual HRQoL outcomes as compared to RC. However, high-quality studies are needed to confirm these findings. Side effects of both treatment approaches should be communicated to the patients as radiochemotherapy is more often characterized with bowel problems and RC with urinary problems [27]. However, recent advances in radiotherapy techniques allow greater dose escalation on the treatment targets, with lower doses to the surrounding tissues, which might result in less toxicity and consequently better HRQoL [58].

Overall, when decision-makers or researchers are looking for evidence in the literature, attention should be paid on the quality of the systematic reviews. Nineteen reviews did not reach a score of 50% on the AMSTAR 2 quality assessment tool. Most shortcomings were noted for a priori protocol writing, using a comprehensive search strategy, performing

selection and extraction in duplicate, providing reasons for full-text exclusion, risk of bias assessment, sources of funding and adequate investigation of publication bias. Recent systematic reviews had higher-quality scores than older reviews, which can be explained by the stricter requirements to comply with the PRISMA guidelines.

The majority of studies addressed the need for well-validated HRQoL measurements and high-quality RCTs or prospective studies that include HRQoL as primary outcome. A recent systematic review by Mason et al. [16] evaluated the current available patient-reported outcomes measurements for MIBC. They concluded that no existing PROM can be considered as most appropriate because of the lack of validation studies for all PROMS in MIBC.

Furthermore, relatively few HRQoL studies have been conducted in patients with MIBC compared to other tumour groups and RCTs for MIBC to date have often omitted HRQoL as an outcome [59, 60]. Although few high-quality evidence exists in this field, 29 reviews were identified in this umbrella review evaluating the impact of curative treatment on HRQoL in MIBC. Future studies should invest more in designing high-quality original studies instead of performing systematic reviews. However, a contributing factor for this lack of research in MIBC is the small investment in BC research. Boormans et al. [61] showed that research in BC was extremely underfunded: in the UK, the total annual research spent on BC is only £216 per new patient—compared to £561 for prostate cancer [62].

Overall, we recommend that researchers conduct validation studies for HRQoL measurements in MIBC and design high-quality RCTs or prospective studies evaluating HRQoL from neoadjuvant treatment to possible adjuvant treatments. In addition, studies should evaluate which specific domains (e.g. urinary, bowel) impact most on patients’ overall HRQoL.

Conclusions

Based on the available literature, we can conclude the following in terms of HRQoL for patients with MIBC who are undergoing curative treatment: (1) there are no HRQoL differences between RARC with extracorporeal urinary diversion and ORC; (2) patients with a neobladder have better overall and physical HRQoL outcomes, but worse urinary outcomes in comparison with ileal conduit patients; (3) bladder-preserving radiochemotherapy showed slightly better urinary and sexual but worse gastro-intestinal HRQoL outcomes in comparison with RC patients. The overall quality of systematic reviews in the field of HRQoL and MIBC is low and more high-quality studies are required to confirm the findings of this review.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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