

Review

Efficacy of pre and rehabilitation in radical cystectomy on health related quality of life and physical function: A systematic review



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ABSTRACT

Objective: The efficacy of prehabilitation or rehabilitation interventions on radical cystectomy (RC) patient reported outcomes (PROs), and patient centered outcome has not yet been thoroughly explored in prior reviews, therefore the aim of this review is to evaluate the efficacy of a single or multi-modal prehabilitation or/and postoperative rehabilitation interventions compared to standard treatment on postoperative complications after RC.

Methods: We performed a three-step search strategy in PubMed, Cinahl, Embase, Cochrane Library, and Web of Science. We used Covidence for the screening of articles, risk of bias assessment, and data-extraction. GRADE was used to assess the risk of bias in outcomes across studies. Where meta-analysis was possible, we used the random effect method due to substantial heterogeneity. The remaining outcomes were summarized narratively

Results: We identified fourteen studies addressing one of the outcomes. None of the studies provided evidence to support that prehabilitation and/or rehabilitation interventions can improve global health related quality of life (HRQoL) in RC surgery or can reduce postoperative complications significantly. However, preoperative and postoperative education in stoma care can significantly improve self-efficacy and we found significant added benefits of sexual counseling to intracavernous injections compared to injection therapy alone. Likewise, an intensive smoking and alcohol cessation intervention demonstrated a significant effect on quit rates. Physical exercise is feasible and improves physical functioning although it does not reduce the postoperative complications.

Conclusions: Currently, no evidence of efficacy of prehabilitation and/or rehabilitation interventions to improve the overall HRQoL or postoperative complications after RC exists. We found evidence that education in stoma care improved self-efficacy significantly. Adequately powered randomized controlled trials (RCTs) are needed to generate high-quality evidence in this field.

Introduction

Bladder cancer is the 10th most commonly diagnosed cancer globally with approximately 550,000 new cases annually.¹ Approximately 2.1% of all cancer deaths are due to bladder cancer (BC),² radical cystectomy (RC) is the first line treatment when patients are diagnosed with muscle

invasive bladder cancer (MIBC), which includes T2-T4aN0M0 or high grade non-MIBC. RC is a highly complex procedure and includes removal of the bladder together with the prostate and seminal vesicles in men, and anterior vaginal wall, uterus and adnexae in women. Both procedures involve extended lymph node dissection and subsequently establishment of a urinary diversion. Radical cystectomy is associated with a

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high rate of postoperative morbidity (e.g., gastro-intestinal issues, infections and stoma injuries) and at least one complication is experienced in 60%–92% of the patients within the first 90 days post-surgery^{3–5} leading to increased patient burden and rates of hospital readmission (30%).^{5,6} The population is generally characterised by older adults (mean age of 68 years) with a high comorbidity index. This high risk population includes 27% of patients who are at severe nutritional risk and 70% are former or current smokers.⁷ Across Europe 30%–40% of all patients who have received RC have undergone neoadjuvant chemotherapy. Frailty is a complex, multidimensional, and cyclical state of diminished physiologic reserve that results in decreased resiliency, adaptive capacity, and increased physical vulnerability. Frailty has been observed in 21.8% of patients affected by urologic cancers who are more than 70 years of age.⁸ Moreover, it is hypothesised that pre- and post-operative physical and diet interventions may be effective to counteract frailty in this high risk population.⁹

In spite of the increased clinical interest in the utility of systematic prehabilitation interventions to modify deficits in health conditions (optimisation, smoking/alcohol nutrition, alcohol and nutrition = SNAP factors) to improve bladder cancer patients' physical and functional outcomes, proof of the utility and validity for improving the surgical outcomes through advances in preoperative care is still evolving. However, the evidence base it still in its infancy to clearly understand the utility and validity of such preoperative care intervention in bladder cancer.^{10–15} In particular, the efficacy of pre-/or rehabilitation interventions on RC patient reported outcomes (PROs), and patient centered outcomes has not yet been critically appraised through existing reviews in this clinical area.

The Centers for Medicare (CMS) define PROs as a self-report measure of any status of a patient's health condition, current functioning, or health behavior that comes directly from the patient, without re-interpretation of the patient's response by a healthcare profession or family caregivers.¹⁶ This definition reflects three key domains of PROs including health-related quality of life, symptoms and symptom burden (e.g., anxiety, depression, distress, severity or bother), and health behaviors and self-care competencies (e.g., smoking, alcohol consumption, diet, exercise, self-care efficacy beliefs).¹⁶ Therefore, the aim of this review is to systematically evaluate the efficacy of a single or multi-modal prehabilitation or/and postoperative rehabilitation interventions on these three dimensions of PROs compared to standard treatment and on postoperative complications after RC.

Methods

Analysis methods and inclusion criteria for this systematic review and meta-analysis were specified in advance and documented in a protocol in compliance with the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' (PRISMA) Statement.¹⁷

The protocol was registered with the Prospero database in November 2018 (CRD42018085915).

Search strategy

Informed by the PICO tool (Population, Intervention, Comparison and Outcomes),¹⁸ a structured search strategy was developed in collaboration with a research librarian at Copenhagen University Hospital - Rigshospitalet. A three-step search strategy was utilised. An initial search for already known and relevant literature in the database PubMed was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the relevant articles. A second search using all identified keywords and index terms were then undertaken across all included databases after having adjusted the controlled vocabulary. Third, the reference lists of all identified relevant articles were then searched for additional studies. The search was carried out from inception until July 2021. The included electronic databases were PubMed, Cinahl, Embase, Cochrane Library and Web of Science. An exemplar search strategy is available in [Appendix 1](#).

Study selection

All publications identified from the searches were uploaded to Covidence systematic review software for removal of the duplicates. Then, all articles (titles and abstract, including full-text screening) were undertaken in according to the pre-determined eligibility criteria.

The title and abstract screening were performed independently by CP, TT NR and SVL and any potentially relevant studies were forwarded to full-text screening. Assessments of full-text studies were conducted independently by NM, BTJ, HG, SVL. All conflicts were resolved by discussion or consulting a third reviewer.

Criteria for considering studies for this review

This review only included randomized controlled trial (RCT) studies that included one or more of the PROs following pre- or rehabilitation interventions in relation to RC: physical activity and physical exercises, nutritional supportive interventions, smoking and alcohol cessation interventions, psychosocial interventions, and self-care interventions that had one of the following outcomes:

1. Health related quality of life (HRQoL),
2. Complications as defined by The Clavien Dindo Classification,
3. Physical function and physical activity,
4. Self-care skills or self-care competencies and efficacy beliefs,
5. Sexual health defined as a state of physical, emotional, mental and social well-being in relation to sexuality,
6. Nutritional status as defined in the included studies,
7. Smoking cessation defined as successful quitting,
8. Alcohol cessation defined as successful quitting, and
9. Depression and Anxiety levels during the intervention period and follow up.

Extraction and analysis of data assessment

Data-extraction was done according to predefined extraction sheets in the protocol by BTJ and SVL in Covidence. Conflicts were resolved by discussion by the two data extractors. The only outcome where data allowed meta-analysis was postoperative complications. The random effect method was used due to substantial heterogeneity. The remaining outcomes were summarized using a narrative synthesis.

Risk of bias and certainty of the evidence

The risk of bias was assessed and guided by the Cochrane Handbook.¹⁹ If blinded outcome assessment was not stated explicitly, the reviewers assessed it as unclear. If no other biases were evident they were rated low risk of bias. For the comparison perioperative nutritional interventions versus standard care with the outcome postoperative complications, the reviewers graded the certainty of the evidence for the five GRADE criteria: Risk of bias, inconsistency, indirectness and imprecision.²⁰

Results

Results of the literature search

The literature search resulted in 9271 hits ([Fig. 1](#)).

Characteristics of included studies

We identified seventeen articles representing 14 individual studies, which fulfilled the inclusion criteria and addressed one or more of the pre-selected outcomes. The majority of the studies evaluated the efficacy of exercise and nutrition ([Table 1](#)).

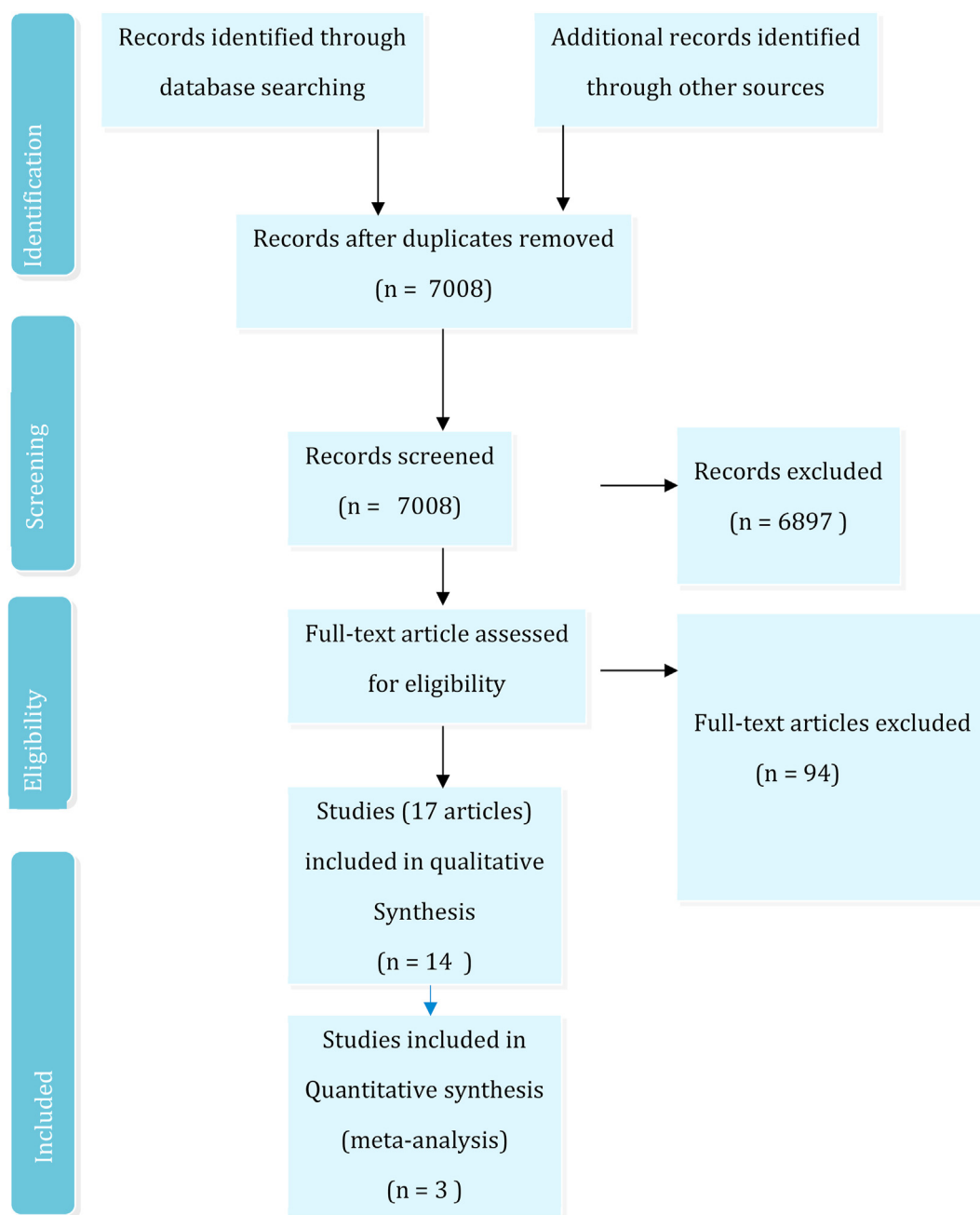


Fig. 1. Prisma flow-chart literature search and selection.

Assessment of risk of bias

The studies from Jensen 2014, 2015, 2016, 2017 are based on the same population. Overall, the studies were rated at a moderate risk of bias. Regarding blinding of participants and personal, all studies were at high risk of bias except Hamilton-Reeves 2018 who double blinded for the nutritional intervention. Few studies described blinding of outcome assessors resulting in unclear risk of bias (Fig. 2). The quality of the evidence was very low for the comparison perioperative nutritional intervention versus standard care with the outcome perioperative complications (Table 2).

Results related to each PICO

Main outcome

PICO 1: What is the efficacy of a single or multi-modal systematic prehabilitation or/and postoperative rehabilitation interventions on HRQoL

compared to standard care?: Four RCT-studies in relation to PRO was identified according to inclusion criteria.^{21–24}

Jensen et al. reported on the efficacy of a multimodal pre and post-rehabilitation intervention on HRQoL after RC as measured by the European Organization for Research and Treatment of Cancer (EORTC)^{21,25} Core Questionnaire 30 (QLQ-C30). This questionnaire was used in combination with the bladder symptom-specific HRQoL, namely the EORTC BLS24 at baseline (14–17 days before surgery) and combined with the EORTC BLM30 at four months post-surgery. The EORTC general cancer HRQoL (QLQ-C30) measured global health, five functional scales (physical, role, emotional, cognitive, and social functioning), three symptom scales (fatigue, pain, and nausea/vomiting) and six single-item scales that evaluate different aspects of cancer care (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Jensen et al. found no impact of physical rehabilitation on global HRQoL. However, the exercise-based intervention did reach statistical

Table 1
Characteristics of included studies.

Author-year	Number of patients I/C	Intervention	Outcome
Titta 2006	29/28	Sexual counselling perioperative	Erectile rehabilitation (index of erectile function (IIEF))
Banerjee 2018	30/30	Exercise preoperative	Complications
Jensen 2014*	50/57	Exercise pre- and postoperative	Physical functioning (cardiopulmonary fitness)
Porserud 2014	9/9	Exercise postoperative	HRQoL (EORTC QLQ C30 + EORTC BLS24 preoperatively and EORTC C30 + EORTC BLM 30 postoperatively)
Jensen 2017*	50/57	Preoperative stoma education	HRQoL (SF36)
Minnella 2019/2021	35/35	Exercise, nutrition, relaxation intervention	Physical functioning (6MWT)
Hamilton-Reeves 2018	14/15	Nutrition perioperative	Complications
Ritch 2019	31/30	Nutrition perioperative	Complications
Deibert 2016	34/31	Nutrition postoperative	nutritional status (BMI, sarcopenia, protein intake)
Jensen 2016*	50/57	Exercise	Complications
Roth 2013	74/83	Nutrition postoperative	Physical functioning (Muscle power)
Jensen 2015*	50/57	Exercise	Complications
Zhou 2019	23/23	Nurse-led multicomponent intervention	nutritional status (resumption of full diet)
Merzaai 2021	2 x 47	Smoking and alcohol cessation intervention perioperative	Physical functioning (distance walked, hours out of bed)
Mohamed 2020	17/8	Educational training perioperative	Self-care skills (stoma self-efficacy scale (SSES))
Kort 2021	23/19 (but data analysed on 17/14)	Nutritional intervention postoperative	Quit rate
			Self-care skills (self-efficacy belief)
			HRQoL (EORTC QLQ C30)

* The study from 2014 and 2017 has the same study population. I = Intervention; C = Control.

significance on HRQoL scales. Moreover, the results identified improved mobilisation and respiratory function (dyspnea) in favour of the intervention group.

Porserud et al. conducted a pilot RCT investigating the feasibility and effects of an exercise programme in patients following RC on HRQoL as a secondary outcome to this study.²² The intervention group took part in a group exercise training programme twice a week over a 12-week period. The intervention group demonstrated improved general HRQoL as measured by the SF 36 compared to the control group ($P = 0.031$) including the role physical domain. At baseline, all of the participants' scores were lower than the 25th percentile of the matched population for five out of the eight SF-36 domains. Thus underscoring that these low scores may emphasize the importance of pre- and rehabilitation after RC. However, this intervention study was not feasible for most of the patients.

Kort et al. examined the effect of a systematic postoperative nutritional intervention (NI) with oral nutrition, supplemental total parenteral nutrition (TPN) compared to a standard care postoperative nutritional strategy after RC on HRQoL.²³ The study was a non-blinded RCT involving forty-two patients undergoing RC for bladder cancer randomly assigned to postoperative NI or standard care. The follow-up period was 12 weeks. The primary outcome was improvement in global HRQoL using the EORTC Quality of Life Questionnaire (EORTC QLQ-C30). The study found that the groups did not differ significantly in HRQoL.

Karl et al. used for the first time the EORTC QLQ-30 scores as primary outcome, when testing an ERAS- protocol vs. standard care after RC.²⁴ HRQoL did not change significantly between postoperative days 3 and 7 and at discharge from hospital in the conservative regimen group, whereas a significant improvement was observed in almost all domains in the ERAS group after surgery group although not in global health.

In summary, the evidence of effect of pre and/or rehabilitation on HRQoL is inconclusive. Jensen found a significant positive impact on domains of HRQoL, which included bowel management, mobilisation and respiratory function (dyspnea), which was likewise Porserud found the same trend. Karl found significant differences in almost all single item subscales. However, none of the studies found an impact on overall HRQoL.

Secondary outcomes

PICO 2: What is the efficacy of a single or multi-modal systematic pre-rehabilitation or/and postoperative rehabilitation interventions on complications

compared to standard treatment?: Six studies looked at the effect of varying interventions provided either preoperatively,^{26,27} peri-operatively^{28,29} or postoperatively^{30,31} on postoperative complications. Postoperative complications were investigated as a primary outcome in two studies^{30,31} while the remaining four studies looked at complications as a secondary outcome.^{26,28,29,32} All of studies ($n = 6$) assessed complications within 30–90 days postoperatively using the Clavien-Dindo classification system as recommended by the major urological societies. Perioperative oral nutrition supplementation (ONS),²⁸ postoperative early enteral nutrition,³¹ postoperative total parenteral nutrition,³⁰ arginine-enriched specialized immunonutrition,²⁹ supervised vigorous intensity aerobic interval exercise²⁶ while Jensen et al. tested an intervention combining preoperative and postoperative physical exercise training with enhanced postoperative mobilisation.^{27,32} Comparisons were standard perioperative care or ONS. The studies were at high or unclear risk of bias, mainly due to unclear description of sequence generation and allocation concealment and lack of blinding of participants, clinicians, and outcome assessors (Fig. 1).

One study at low risk of bias looking at the effect of postoperative total parenteral nutrition (TPN) from POD 1 and lasting five days versus oral alimentations from POD 1 on postoperative complications as a primary outcome found significantly more complications in the intervention group, 69% versus 49%, $P = 0.013$.³⁰ This effect was driven by a significantly higher number of infectious complications in the intervention group 32% versus 11%, $P = 0.001$.³⁰ The most prevalent infections were pyelonephritis, urosepsis, pneumonia, fever of unknown origin and wound infections.³⁰

Hamilton-Reeves who tested the effect of arginine-enriched specialised immunonutrition versus ONS from five days before to five days after RC on complications as a secondary outcome found a significant reduction in complications at 90 days, %-difference between groups -33 (95% CI, -70 – 5.7) while there was no difference between groups at 30 days, -2 (95% CI, -36 – 33). The effect at 90 days appeared largely related to a decrease in antibiotic use, -39 (95% CI, -77 – 0.94).²⁹ The study was at low risk of bias, however only included men and the sample was small ($n = 29$) as reflected in the broad confidence intervals.

None of the remaining studies testing preoperative vigorous exercises, perioperative ONS, perioperative postoperative early enteral nutrition, physical exercise training with enhanced postoperative

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Banerjee 2018	+	+	-	+	+	+	+
Deibert 2016	-	-	-	-	+	+	+
Hamilton-Reeves 2018	+	+	+		-	-	+
Jensen 2014	+	+	-		+	+	+
Jensen 2015	+	+	-		+	+	+
Jensen 2016	+	+	-		+	+	+
Jensen 2017	+	+	-		+	+	+
Karl 2014			-			-	+
Kort 2021	+	+	-			-	+
Merzaai 2021	+	+	-	+	+	+	+
Minnella 2019	+	+	-	-	-	+	+
Mohammed 2021	+		-				+
Porserud 2014	+	-	-	+	-	+	+
Ritch 2019	+	+	-		+	+	+
Roth 2013	+	+	-		+	+	+
Titta 2006	-	-	-	-	-		+
Zhou 2019	+		-		+		+

Fig. 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study. Red = high risk, blank = unclear and green = low risk of bias.

mobilisation detected any differences between groups in postoperative complications. Overall, complications were minor (grade 1–2 according to the Clavien–Dindo) across groups in all studies.

In summary, the meta-analysis for pre- and postoperative nutritional interventions showed no statistical significant difference in postoperative complications ($P = 1.0$, P5% CI, 0.69–1.46) and the quality of the evidence was very low (Table 2) (Fig. 3).

PICO 3: What is the efficacy of a single or multi-modal systematic prehabilitation and/or postoperative rehabilitation interventions on physical function compared to standard treatment?: There were five

publications,^{22,26,27,32,33} which explored the impact of multi-modal prehabilitation and/or rehabilitation interventions on physical function among people affected by bladder cancer. Physical function outcomes included: cardiopulmonary fitness²⁶ hours out of bed, walking distance,³² muscle leg power (W/kg),²⁷ 6-min walk test (6MWT)^{22,33} and the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire.³³ There was significant heterogeneity in measuring the physical function outcomes across the studies included. Banerjee et al.,²⁶ conducted a 1:1 feasibility RCT ($n = 60$) which tested a vigorous intensity aerobic interval exercise intervention in the prehabilitation setting and compared this to standard care. The results identified improvements in cardiopulmonary fitness compared to the control group.²⁶ Improvements have been reported in distance walked during the first seven days post-operatively in favour of the prehabilitation interventions,^{22,32} and at 14 weeks, and 1 year.²² No difference was reported for “hours out of bed” between the intervention and control group.³² Jensen et al. also reported benefit of prehabilitation intervention on muscle leg power (W/kg) at the time of surgery.²⁷ Other reported physical function benefits of prehabilitation for the 6MWT at four weeks and eightweeks after surgery, but no statistically significant difference in the 6MWT during the pre-operative phase, or on self-report physical activity levels (using the CHAMPS instrument) over time.³³

In summary, physical pre and rehabilitation is feasible and effective, however, long-term results lacks.

PICO 4: What is the efficacy of a single or multi-modal systematic prehabilitation and/or postoperative rehabilitation interventions on Self-care or self-efficacy in stoma-care compared to standard treatment?: Three studies focused on involving patients to obtain self-efficacy.^{34–36} Jensen and colleagues evaluated the efficacy of their single-modal prehabilitation intervention in stoma-care compared to standard treatment with a sample of 107 radical cystectomy patients as part of a parent randomised controlled trial.³⁷ The intervention group received preoperative stoma education designed to increase knowledge and understanding of stoma care and living with a stoma, as well as training and practice in stoma care and changing appliances. Researchers used the Urostomy Education Scale (UES), which has demonstrated good reliability and validity(ref). Higher UES scores correspond to greater self-efficacy and independence with stoma care and coping with stoma measured at days 35, 120, and 365 post-operatively. The intervention group reported higher mean UES scores for most self-care stoma skills at each postoperative time point compared to the control group, indicating increasing self-efficacy and agency for independence in stoma self-care at all-time points. In contrast, the control group's UES scores consistently decreased over the same time points.

Zhou et al. investigate the effect of a nurse-led multicomponent intervention focused on postoperative ostomy self-management and stoma related quality of life. Forty-six patients, who underwent RC participated in the trial. Participants in the control group received routine care over a six-month period following surgery, while those in the experimental group received a nurse-led, multicomponent, structured intervention delivered by a specialist ostomy care team, monthly. Teaching included a practical demonstration that included a full appliance change. The sessions also emphasised the importance of the patient's physical care and the need of ongoing emotional support, ostomy related complications, self-efficacy, and stoma health-related quality of life in patients with an ileal conduit.³⁶ Stoma Self-efficacy Scale (SSES) and the City of Hope Quality of Life-Ostomy (COHQOL-O) questionnaire were used to assess self-efficacy in stoma care At six months, the incidence of ostomy complications was statistically significantly lower in the experimental group as compared to the control group (4.35% versus 30.43%). SSES score was significantly higher (indicating greater self-efficacy in stoma care) (107.13 ± 11.87 versus 85.65 ± 12.87), and the mean COHQOL-O score was also significantly higher in the experimental group, indicating higher stoma related quality of life (154.48 ± 16.01 versus 138.26 ± 13.42).

Muhammed et al. investigated the acceptability and feasibility of an educational and training experiential intervention to RC patients with

Table 2
Summary of findings.

Perioperative nutritional interventions compared to standard care for patients undergoing radical cystectomy						
Patient or population: patients undergoing radical cystectomy						
Setting:						
Intervention: perioperative nutritional interventions						
Comparison: standard care						
No. of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)		Difference	Certainty	What happens
Postoperative complications (Complications) assessed with: Clavien Dindo follow-up: mean 90 days No. of participants: 349 (4 RCTs)	RR 1.00 (0.69–1.46)	55.0%	55.0% (38–80.3)	0.0% fewer (17,1 fewer to 25,3 more)	⊕○○○ Very low ^{a,b}	

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI, confidence interval; RR, risk ratio; RCT, randomized controlled trial.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

^a Parenteral and enteral nutritional interventions are compared.

^b Hamilton-Reeves was a pilot study, reflected in the small sample size and wide CI.

focus on treatment decision-making and post-operative self-care.³⁵ Twenty-five patients were randomised to a control group ($n = 8$) or intervention ($n = 17$). The intervention was an intensive nurse-led session on education related to specifically to patients affected by MIBC. The control group received diet and nutrition education only. Self-efficacy outcomes were completed at baseline and at one-month post-intervention. The results showed acceptable recruitment (58%) and retention rates (68%). The intervention group reported increased knowledge (82% versus 50%), improved decisional support (64% versus 50%), improved communication (73% versus 50%), and increased confidence in treatment decisions (73% versus 50%) compared to the control group. Patients in the control group reported improved diet (50% versus 27%) as well as maintaining a healthy lifestyle (67% versus 45%) compared to intervention. Patients in the intervention group also reported a significant decrease in cancer related worries and increased self-efficacy beliefs over time compared to the control group. The intervention was feasible, acceptable, and showed a potential for inducing desired changes in cancer related worries and self-efficacy beliefs.

In summary, there are clear indications that pre- and post-operative education can improve self-efficacy, stoma related complications and stoma related quality of life although the evidence is sparse and developing.

PICO 5: What is the efficacy of a single or multi-modal systematic prehabilitation and/or postoperative rehabilitation interventions on sexual health compared to standard treatment?: Only one study was identified comparing the utility of sexual counseling in patients treated with intracavernous injection (ICI) therapy for erectile dysfunction (ED) after non-nerve-sparing cystectomy.³⁸ The goal of this study was to examine the added benefits of sexual counseling to intracavernous injections (ICI). Fifty-seven patients with ED diagnosis following radical prostatectomy or cystectomy were randomised to two groups; the first group included 29 patients who received sexual counseling and ICI therapy; the second group included 28 patients and received ICI therapy only. All participants were shown how to administer ICI (self-injection training test) on study enrollment visit (mean time from surgery was 29 days, range 20–41). Sexual counseling focuses on four steps: A: assessing patient's and intimate partner's sexual history and behaviors and couples' satisfaction in ICI therapy and related challenges in ICI therapy administration; B: a clinical interview with both partners to address emerging issues and challenges e.g. managing drug resistances and compliance, facilitating couple's communication about sexual problems and forming "therapeutic alliance" between couple and therapeutic; C: a telephone counseling to

adjust dose and to facilitate home Sildenafil test. D; a short-term sexual therapy regarding the couples' sexual behaviors and relationship. Pre and post-intervention assessments (3, 6, 9, 12, and 18 months after surgery) showed significant impact of ICI-oriented sexual counseling on ICI efficacy ($P < 0.05$). Similar beneficial effect of the intervention was observed in compliance, responders rate, decreased the dropout rate.

In summary, there are significant added benefits of sexual counseling to intracavernous injections compared to injection therapy alone.

PICO 6: What is the efficacy of a single or multi-modal systematic prehabilitation and/or postoperative rehabilitation interventions on nutritional status compared to standard treatment?: Three studies were identified that addressed the efficacy of interventions on nutritional status.^{28–30} Surgery induces the surgical stress response and can lead to a catabolic state postoperatively. This breakdown of muscle protein and fat puts the patient at a higher risk of malnutrition. It has been recognised that inadequate nutritional status prior to major surgery is associated with postoperative complications and poorer outcomes.²⁹

The study by Roth et al. compared the use of total parenteral nutrition (TPN) plus oral intake to a control group that received oral nutrition alone.³⁰ In total, 157 patients were randomly assigned to the two groups, group A (receiving TPN plus oral) including 74 patients, and the control group B (receiving the standard of oral alone) including 83 patients. The primary outcome of this study was to evaluate the occurrence of postoperative complications. Secondary outcomes were time to recovery of bowel function, biochemical nutritional (serum albumin, serum pre-albumin, serum total protein). Postoperative complications occurred in 51 patients (69%) in group A and in 41 patients (49%) in group B ($P = 0.013$), a difference resulting from group A having more infectious complications than group B (32% versus 11%; $P = 0.001$). Serum pre-albumin and serum total protein were significantly lower in group B on postoperative day 7 but not on postoperative day 12. There was no difference in time to gastrointestinal recovery.

To understand the effect of oral nutrition on the body composition of a patient undergoing a radical cystectomy, Ritch et al. used the status of sarcopenia as an indicator of postoperative morbidity.²⁸ In a RCT study of 61 patients, the final analysis consisted of 31 subjects who received ONS compared to 30 subjects, who received multivitamins (MVI) for 3–4 weeks prior and three weeks post-surgery. The results showed statistical significance in the decrease in weight and BMI ($P = 0.04$) in the MVI group. The reduction of protein intake and amount of muscle mass loss was greater in the MVI group ($P = 0.01$). Sarcopenia increased by 20% ($P = 0.01$) in the MVI group as well. Additionally, although statistical

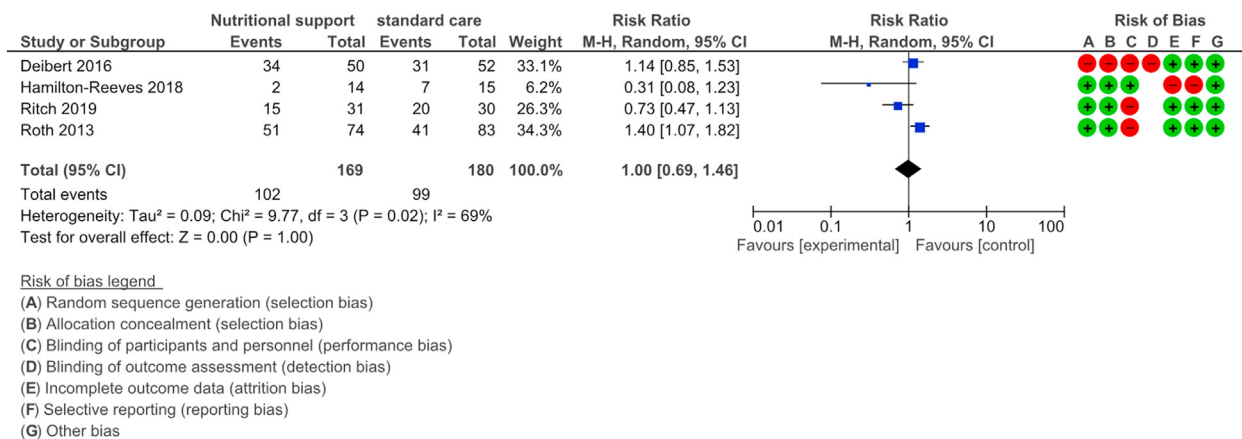


Fig. 3. Forest plot of comparison: Perioperative nutritional intervention versus standard care. Outcome: Number of patients with postoperative complications within 90 days.

significance was not reached, overall complication rates, 30-day hospital-free days and readmissions were lower in the ONS group.

Hamilton-Reeves et al. examined the acute inflammatory response and arginine status of RC patients.²⁹ Patients were random assignment into received specialised immunonutrition (SIM arm) and compared to the control group receiving ONS. Each group consumed three cartons per day of their respective supplement for five days before and five days after their surgery. Outcomes measured were Th1–Th2 balance, plasma interleukin-6, and plasma amino acids, as well as body composition. The results suggested that SIM has a greater influence on these inflammatory responses, restoring the Th1–Th2 balance and therefore potentially decreasing the vulnerability to complications.

In summary, the results indicate support for enteral nutritional intervention prior to undergoing RC. Two studies showed a reduction in complications when early supplemented enteral nutrition was introduced, although statistical significance was not reached, overall complication rates, 30-day hospital-free days and readmissions were lower in the ONS group. The results suggested that SIM has a greater influence on these inflammatory responses, restoring the Th1–Th2 balance and therefore potentially decreasing the vulnerability to complications. Of note, in one study risk of infections increased when parenteral nutrition was introduced.

PICO 7: What is the efficacy of a single or multi-modal systematic prehabilitation and/or postoperative rehabilitation interventions on smoking and/or alcohol cessation compared to standard treatment?: One RCT was identified reporting quit rates after an intensive smoking and/or alcohol cessation intervention starting shortly before RC and continuing five weeks after surgery. In this study, 104 patients were randomised to either a six-week smoking and/or alcohol cessation intervention or standard care. Patients in the intervention group had five counselling sessions with trained counselors and they were offered nicotine replacement therapy during the intervention period free. The study found that the self-reported abstinence rate after the six-week intervention was 51% in the intervention group and 27% in the control group.³⁹ The one RCT addressing a combined smoking and/or alcohol cessation intervention found that the self-reported abstinence rate after the six-week intervention was 51% in the intervention group and 27% in the control group.³⁹

Pico 7 and 8 was collapsed due overlapping studies.

PICO 9: What is the efficacy of a single or multi-modal systematic prehabilitation or/and postoperative rehabilitation interventions on depression and anxiety compared to standard treatment?: No studies found.

Discussion

The aim of this systematic review was to evaluate the efficacy of a single or multi-modal systematic prehabilitation or/and postoperative

rehabilitation interventions on these three dimensions of PROs and postoperative complications compared to standard treatment after RC.

None of the included studies was able to provide evidence to support that pre and/or rehabilitation interventions can improve *global* HRQoL regardless of type of questionnaire. Apart from lack of statistical power, this may be due to the inconsistency and lack of agreement between urological societies on how to report HRQoL in a robust manner in clinical trials. However, The study by Karl et al. used HRQoL as primary outcome²⁴ when testing the impact of ERAS protocol versus standard care. In almost all sub-scales, the ERAS-group reported significant higher score in almost all domains. In this study complications were secondary outcome opposed to all other studies in the early days of ERAS and postoperative morbidity was lower in the early recovery after surgery group, which may reflect the higher HRQoL scores.

The evolving focus on prehabilitation as the open window of opportunity to optimize and modify the individual health conditions have provided accumulating evidence that both pre and rehabilitation have a future role in an extended ERAS RC-pathway.^{11,33} A recent systematic review by Briggs et al. with the objective to evaluate the therapeutic validity and efficacy of prehabilitation exercise programs undertaken before urologic cancer surgery emphasised that pre- and/or post-operative measures of cardiorespiratory fitness and muscle capacity demonstrated significant improvement in at least one outcome.¹³ Like in this systematic review, no pre and/or rehabilitation in RC surgery has so far demonstrated reduction in postsurgical complications¹¹ (Fig. 1). This may also be explained by underpowered sample sizes in the four RCT performed so far, and the fact that pre and/or rehabilitation studies in general lacks personalised recommendations.^{26,32,33,40} In the literature only one out of six identified prehabilitation studies in RC populations provided patients with the opportunity to choose between a wide ranges of exercises rather than prescribing a single regimen-like “one fits it all” although this study was not a RCT-study.⁴¹ Moreover, none offered direct tailoring of exercise and nutritional intervention on an individual basis, which potentially could enhance the autonomy of patients within pre and rehabilitation and improve adherence through a tailored and target program, which must be a goal for future studies.

Single or multi-modal systematic prehabilitation or/and post-operative rehabilitation interventions to improve stoma self-care were found to be effective and sustainable up to one year post surgery in the study by Jensen et al.³⁴ Zhou et al.³⁶ documented that a nurse-led multicomponent intervention reduced ostomy-related complications, improved the self-efficacy level and stoma related quality of life six months post-surgery. The two studies are not comparable due to different time perspective and outcome, but both studies points towards stoma educational interventions pre and postoperative are effective and promote self-efficacy thus beneficial for the patients, reduce anxiety and in

line with findings in colorectal surgery.⁴² Mohamed et al. tested a global educational intervention to MIBC patients before surgery; control only received information regarding nutrition.³⁵ An important result from this study was that patients in the intervention group reported a significant decrease in cancer worries and increases in self-efficacy beliefs over time compared to the control group. The intervention was feasible, acceptable, and showed a potential for inducing desired changes in cancer worries and self-efficacy beliefs, which has not been shown before and is²⁹ promising and further research in this field is warranted.

RC impairs gut function and metabolism due to the reconstruction and creation of, for example, an uro-stoma, which re-routes the urine through intestinal segments, resulting in infection, rapid muscle wasting and other complications. Many complications associated with RC are initiated by exaggerated adaptive immune suppression and inflammatory responses, especially infections and muscle wasting.²⁹ However, the Enhanced Recovery after Surgery (ERAS) pathways promote early post-operative oral nutrition as one strategy to counteract the stress response.⁴³ Early enteral nutritional interventions as opposed to parenteral regime are superior in order to reduce risk of complications. A significant increased risk of infectious complications was found when using parenteral supplements.³⁰ The nutritional component of pre and rehabilitation functions complement the exercise regimen. In particular, the protein needs of the pre- and postsurgical patient must be addressed in future studies to compensate for the catabolic effects of illness, and the additional amino acids required for postoperative healing as seen in the study by Ritch.^{28,44} Ritch successfully demonstrated to counteract sarcopenia by ways of an ONS regime; the lack of protein intake and the amount of muscle mass loss was greater in the control ($P = 0.01$) and sarcopenia increased by 20%.²⁸ Recently, a RCT of patients with under ERAS care, also found that 14 days of supplementation with high-protein ONS before surgery resulted in fewer serious postoperative complications.⁴⁵ These results instill optimism and provision of adequate total protein intake should be the focus of nutritional prehabilitation and rehabilitation interventions. Especially, when considering less than 50% of older adults do not meet the minimal dietary protein requirements established for healthy individuals.⁴⁶

This review provided little evidence of post-operative rehabilitation interventions on sexual health after RC. Titta et al. showed significant impact of ICI-oriented sexual counseling on ICI efficacy, compliance, responder's rate, decreased the dropout rates, but several limitations exist.³⁸ These include, the heterogeneity of the study participants, the added burden of urinary diversion procedure which may intensify the psychological impact of surgery on sexual function, and study timeline (mean time from surgery was 29 days) which may have overlooked the longer physical and functional recovery period needed for patients undergoing RC. Additionally, no information was provided on same-sex couples and sexual orientation-tailored consultations to address their specific needs. More research is needed to address these gaps like psychological issues and use of sex therapies in treating sexual dysfunction among RC patients and their partners.

In general surgery, intensive smoking-cessation interventions 6–8 weeks before elective surgery reduces the risk of postoperative complications with approximately 50%.^{47,48} Daily smoking increases the risk of developing wound complications, general infections and pulmonary complications. Likewise it reduces the immune capacity leading to an increased risk of infection and impaired wound healing.⁴⁹ Cigarette smoking is the best-established risk factor for bladder cancer development, increasing the risk fivefold⁵⁰ and smoking status is significantly associated with disease recurrence. Quitting for more than 10 years decreases the risk of recurrence⁵¹ and as successful quitting is most likely to happen when smoking cessation is offered at the time of bladder cancer diagnosis,⁵² attention should be paid to the importance of encouraging bladder cancer patients to quit as early as possible. Smoking cessation will benefit the health of the patient even in the short term, underlining the need to support patients undergoing RC to quit smoking,^{53,54} while continued smoking is associated with increased risk of surgical

complications after RC.^{55,56}

The threshold for an increased risk of complications may be as low as >2 drinks per day.⁵⁷

The use of standardised multidimensional instruments should be used to screen patients undergoing RC to identify potentially modifiable risk factors that can be included in future targeted and tailored prehabilitation interventions.⁵⁸ When screening for alcohol consumption recall bias is often experienced and using a seven-day time-line follow back interview is recommended.⁵⁹ High alcohol consumption reduces the immune capacity leading to an increased risk of infection and impaired wound healing.^{60,61} In addition, risky drinking increases the endocrine stress response to surgery, leading to deterioration of existing conditions, which thus increases the risk of postoperative complications.

Despite the well-known burden of impairments in MIBC patients, psychosocial interventions remains and understudied field. The lack of RCTs assessing e.g. anxiety and depression in RC patients is concerning given the high documented unmet supportive care needs in this patient group.⁶² Emotional and social support interventions could help patients in emotional expression, reduce the sense of fear and isolation, by identifying unmet needs and accepting losses and changes. The importance of cognitive-behavioral interventions focusing on depression and anxiety should be a future common engagement in the bladder cancer community.

Conclusions

There is currently no evidence of efficacy of pre and/or rehabilitation interventions to improve overall HRQoL although some evidence support effect in single items like physical function and respiratory function (dyspnea). Moreover, pre and/or rehabilitation interventions have so far not been shown to be effective in reducing postoperative complications 90 days after RC surgery. However, physical pre and/or rehabilitation interventions are effective, although long-term insights in to possible benefits are still in its infancy. Enteral nutrition reduce risk such as sarcopenia, frailty and increase benefits to the RC patient, but are conflicted due to increased infections, and some caution should be taken in practice. Pre- and postoperative stoma education is effective and sustainable over time and impacts positively on stoma HRQoL and self-efficacy. Finally, the review showed little evidence of post-operative rehabilitation interventions to improved sexual health. Intensive smoking and alcohol cessation interventions significantly improved quit rates, and future studies evaluating the efficacy on postoperative complications and HRQoL are recommended. A future focus should design interventions to reduce depression or anxiety given the dearth of focus to date in this clinical area.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Asia-Pacific Journal of Oncology Nursing* at <https://doi.org/10.1016/j.apjon.2022.02.008>.

Declaration of competing interest

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