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[Intervention Review]

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy

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ABSTRACT

Background

Radical cystectomy (RC) is the primary surgical treatment for muscle-invasive urothelial carcinoma of the bladder. This major operation is typically associated with an extended hospital stay, a prolonged recovery period and potentially major complications. Nutritional interventions are beneficial in some people with other types of cancer and may be of value in this setting too.

Objectives

To assess the effects of perioperative nutrition in people undergoing radical cystectomy for the treatment of bladder cancer.

Search methods

We performed a comprehensive search using multiple databases (Evidence Based Medicine Reviews, MEDLINE, Embase, AMED, CINAHL), trials registries, other sources of grey literature, and conference proceedings published up to 22 February 2019, with no restrictions on the language or status of publication.

Selection criteria

We included parallel-group randomised controlled trials (RCTs) of adults undergoing RC for bladder cancer. The intervention was any perioperative nutrition support.

Data collection and analysis

Two review authors independently assessed studies for inclusion, extracted data, and assessed risk of bias and the quality of evidence using GRADE. Primary outcomes were postoperative complications at 90 days and length of hospital stay. The secondary outcome was mortality up to 90 days after surgery. When 90-day outcome data were not available, we reported 30-day data.

Main results

The search identified eight trials including 500 participants. Six trials were conducted in the USA and two in Europe.

1. Parenteral nutrition (PN) versus oral nutrition: based on one study with 157 participants, PN may increase postoperative complications within 30 days (risk ratio (RR) 1.40, 95% confidence interval (CI) 1.07 to 1.82; low-quality evidence). We downgraded the quality of evidence for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious

imprecision. This corresponds to 198 more complications per 1000 participants (95% CI 35 more to 405 more). Length of hospital stay may be similar (mean difference (MD) 0.5 days higher, CI not reported; low-quality evidence).

2. Immuno-enhancing nutrition versus standard nutrition: based on one study including 29 participants, immuno-enhancing nutrition may reduce 90-day postoperative complications (RR 0.31, 95% CI 0.08 to 1.23; low-quality evidence). These findings correspond to 322 fewer complications per 1000 participants (95% CI 429 fewer to 107 more). Length of hospital stay may be similar (MD 0.20 days, 95% CI 1.69 lower to 2.09 higher; low-quality evidence). We downgraded the quality of evidence of both outcomes for very serious imprecision.

3. Preoperative oral nutritional support versus normal diet: based on one study including 28 participants, we are very uncertain if preoperative oral supplements reduces postoperative complications. We downgraded quality for serious study limitations (unclear risk of selection, performance, attrition and selective reporting bias) and very serious imprecision. The study did not report on length of hospital stay.

4. Early postoperative feeding versus standard postoperative management: based on one study with 102 participants, early postoperative feeding may increase postoperative complications (very low-quality evidence) but we are very uncertain of this finding. We downgraded the quality of evidence for serious study limitations (unclear risk of selection and performance bias) and very serious imprecision. Length of hospital stay may be similar (MD 0.95 days less, CI not reported; low-quality evidence). We downgraded the quality of evidence for serious study limitations (unclear risk of selection and performance bias) and serious imprecision.

5. Amino acid with dextrose versus dextrose: based on two studies with 104 participants, we are very uncertain whether amino acids reduce postoperative complications (very low-quality evidence). We are also very uncertain whether length of hospital stay is similar (very low-quality evidence). We downgraded the quality of evidence for both outcomes for serious study limitations (unclear and high risk of selection bias; unclear risk of performance, detection and selective reporting bias), serious indirectness related to the patient population and very serious imprecision.

6. Branch chain amino acids versus dextrose only: based on one study including 19 participants, we are very uncertain whether complication rates are similar (very low-quality evidence). We downgraded the quality of evidence for serious study limitations (unclear risk of selection, performance, detection, attrition and selective reporting bias), serious indirectness related to the patient population and very serious imprecision. The study did not report on length of hospital stay.

7. Perioperative oral nutritional supplements versus oral multivitamin and mineral supplement: based on one study with 61 participants, oral supplements compared to a multivitamin and mineral supplement may slightly decrease postoperative complications (low-quality evidence). These findings correspond to 135 fewer occurrences per 1000 participants (95% CI 256 fewer to 65 more). Length of hospital stay may be similar (low-quality evidence). We downgraded the quality of evidence of both outcomes for study limitations and imprecision.

Authors' conclusions

Based on few, small and dated studies, with serious methodological limitations, we found limited evidence for a benefit of perioperative nutrition interventions. We rated the quality of evidence as low or very low, which underscores the urgent need for high-quality research studies to better inform nutritional support interventions for people undergoing surgery for bladder cancer.

PLAIN LANGUAGE SUMMARY

Nutrition support for people having an operation for bladder cancer

Review objective

To assess the effects of perioperative nutrition in participants undergoing an operation for treating bladder cancer.

Background

Some people with advanced bladder cancer require an operation called a radical cystectomy to remove their bladder, which has a risk of complications after surgery.

Some people who have bladder cancer may have difficulties with eating before or after the operation and may lose weight and be malnourished. In this review, we wanted to see if providing additional nutrition is of benefit compared to waiting for people to eat ordinary food.

Study characteristics

The evidence is current up to 22 February 2019. There were eight studies conducted including 500 people in hospital. There were seven different ways in which nutrition was given.

Key results

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy (Review)

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1. Feeding into a vein versus oral nutrition: based on one study that included 157 people, we found that feeding into a vein may increase complications after surgery. However, there may be little or no difference in length of hospital stay.

2. Immuno-enhancing nutrition versus standard supplements: immuno-enhancing nutrition has high levels of nutrients that are thought to improve the immune function and was given in one study that included 29 people. We found that this form of nutrition may decrease complications 90 days after surgery, but may have little effect on length of hospital stay.

3. Preoperative oral nutrition support versus diet: based on one study that included 28 people, we are uncertain if oral supplements before surgery improve complications after surgery. Length of hospital stay was not reported.

4. Early postoperative feeding versus standard care: based on one study that included 102 people, early postoperative feeding may increase postoperative complications after surgery, but we are very uncertain of this finding. Length of hospital stay may be similar.

5. Amino acids versus dextrose: amino acids are the building blocks of proteins and dextrose is sugary water. From two studies that included 104 people, we are uncertain whether complications may be reduced. Length of hospital stay may be similar.

6. Branch chain versus dextrose: branch chain are a type of amino acid. From one study that included 19 people, we are very uncertain whether complication rates are similar. Length of hospital stay was not reported.

7. Perioperative oral nutritional supplements versus multivitamin and mineral supplement: from one study that included 61 people, oral supplements compared to a multivitamin and mineral supplement may slightly decrease postoperative complications. Length of hospital stay may be similar.

Certainty of the evidence

The certainty of the evidence for all outcomes in this review was low or very low, meaning that the true effect may be very different or is likely very different from what we found.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Postoperative parenteral nutrition compared to oral nutrition alone for the treatment of bladder cancer by radical cystectomy

Postoperative parenteral nutrition compared to oral nutrition alone for the treatment of bladder cancer by radical cystectomy

Participants: people with bladder cancer who have had a radical cystectomy

Settings: University Hospital Bern, Switzerland

Interventions: parenteral nutrition

Control: oral nutrition with Ringer's lactate solution

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with oral nutrition alone	Risk difference with postoperative parenteral nutrition
Complications Follow-up: 30 days	157 (1 RCT)	⊕⊕⊕⊕ Low ^{a,b}	RR 1.40 (1.07 to 1.82)	Study population 494 per 1000	 198 more per 1000 (35 more to 405 more)
Length of hospital stay	157 (1 RCT)	⊕⊕⊕⊕ Low ^{a,c}	—	The mean length of hospital stay was 15.5 days	MD 0.5 days more (not reported)
Mortality Follow-up: 30 days	157 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,d}	RR 1.12 (0.07 to 17.62)	Study population 12 per 1000	 1 more per 1000 (11 fewer to 200 more)

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

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.

- ^aDowngraded one level due to study limitations (unclear risk of selection, performance and selective reporting bias).
^bDowngraded one level for serious imprecision due to wide confidence intervals that cross assumed threshold of clinical importance.
^cDowngraded one level for suspected serious imprecision (unable to calculate confidence interval).
^dDowngraded two levels for very serious imprecision with very wide confidence interval.

Summary of findings 2. Immunonutrition compared to standard nutritional supplements for the treatment of bladder cancer by radical cystectomy

Immunonutrition compared to standard nutritional supplements for the treatment of bladder cancer by radical cystectomy

Participants: people with bladder cancer who have had a radical cystectomy

Settings: University Hospital Kansas, USA

Interventions: immuno-enhancing nutritional supplement

Control: standard nutritional supplement

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard nutritional supplements	Risk difference with Immunonutrition
Complications Follow-up: 90 days	29 (1 RCT)	⊕⊕⊕⊖ Low^a	RR 0.31 (0.08 to 1.23)	Study population 460 per 1000	 322 fewer per 1000 (429 fewer to 107 more)
Length of hospital stay	29 (1 RCT)	⊕⊕⊕⊖ Low^a		The mean length of hospital stay was 6.1 days	MD 0.2 days fewer (1.69 fewer to 2.09 more)
Mortality Follow-up: 30 days	29 (1 RCT)	⊕⊕⊕⊖ Low^a	RR approximately 1 (no events)	Study population 0 per 1000	 unable to calculate

*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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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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.

^aDowngraded two levels for very serious imprecision with very wide confidence interval.

Summary of findings 3. Preoperative oral nutritional support compared to normal diet for the treatment of bladder cancer by radical cystectomy

Preoperative oral nutritional support compared to normal diet for the treatment of bladder cancer by radical cystectomy

Participants: people with bladder cancer who have had a radical cystectomy

Settings: Hospital, Turin, Italy

Interventions: oral nutritional supplements

Control: normal diet

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with normal diet	Risk difference with Preoperative oral nutritional support
Complications Follow-up: 30 days	28 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	RR 0.89 (0.18 to 4.51)	Study population 188 per 1000	21 fewer per 1000 (154 fewer to 658 more)
Length of hospital stay – not measured	—	—	—	—	—
Mortality Follow-up: 30 days	28 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	RR approximately 1 (no events)	Study population 0 per 1000	Unable to calculate

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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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.

^aDowngraded one level due to study limitations (unclear risk of selection, performance, attrition and selective reporting bias).

^bDowngraded two levels for very serious imprecision with very wide confidence interval.

Summary of findings 4. Early postoperative feeding compared to standard management for the treatment of bladder cancer by radical cystectomy

Early postoperative feeding compared to standard management for the treatment of bladder cancer by radical cystectomy

Participants: people with bladder cancer who have had a radical cystectomy

Settings: 2 hospitals, USA

Interventions: early enteral feeding after surgery

Control: standard care

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with standard management	Risk difference with early postoperative feeding
Complications Follow-up: 30 days	102 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b}	RR 1.14 (0.85 to 1.53)	Study population 596 per 1000	 83 more per 1000 (89 fewer to 316 more)
Length of hospital stay	102 (1 RCT)	⊕⊕⊕⊕ Low ^{a,c}	—	The mean length of hospital stay was 9.7 days	MD 0.95 days fewer (unable to calculate CI)
Mortality Follow-up: 30 days	102 (1 RCT)	⊕⊕⊕⊕ Low ^{a,c}	RR 0.52 (0.10 to 2.71)	Study population 38 per 1000	 19 fewer per 1000 (35 fewer to 72 more)

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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^aDowngraded one level for study limitations (unclear risk of selection and performance bias).

^bDowngraded two levels for very serious imprecision with very wide confidence interval.

^cDowngraded one level for serious imprecision (unable to calculate confidence interval).

Summary of findings 5. Amino acid solution, alone or in combination with dextrose compared to dextrose solution for the treatment of bladder cancer by radical cystectomy

Amino acid solution, alone or in combination with dextrose compared to dextrose solution for the treatment of bladder cancer by radical cystectomy

Participants: people with bladder cancer who have had a radical cystectomy

Settings: hospital, USA

Interventions: amino acid solutions

Control: dextrose

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with dextrose solution	Risk difference with amino acid solution, alone or in combination with dextrose
Complications Follow-up: 30 days	104 (2 RCTs)	⊕⊕⊕⊕ Very low ^{a,b,c}	RR 0.77 (0.32 to 1.82)	Study population 200 per 1000	 46 fewer per 1000 (136 fewer to 164 more)
Length of hospital stay	44 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	—	The mean length of hospital stay was 32 days	MD 0.5 days fewer
Mortality Follow-up: 30 days	60 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	RR approximately 1 (no events)	Study population 0 per 1000	 Unable to calculate

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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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.

^aDowngraded one level due to study limitations (unclear and high risk of selection bias; unclear risk of performance, detection and selective reporting bias).

^bDowngraded one level due to serious indirectness related to patient population.

^cDowngraded two levels due to very serious imprecision with very wide confidence intervals.

Summary of findings 6. Branch chain amino acids compared to dextrose for the treatment of bladder cancer by radical cystectomy

Branch chain amino acids compared to dextrose for the treatment of bladder cancer by radical cystectomy

Participants: people with bladder cancer who have had a radical cystectomy

Settings: hospital, USA

Interventions: branch chain amino acids

Control: dextrose

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with dextrose	Risk difference with branch chain amino acids
Complications Follow-up: 30 days	19 (1 RCT)	⊕⊕⊕⊕ Very low ^{a,b,c}	RR approximately 1 (no events)	Study population 0 per 1000	Unable to calculate
Length of hospital stay – not assessed	—	—	—	—	—
Mortality – not assessed	—	—	—	—	—

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

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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.

^aDowngraded one level due to study limitations.

^bDowngraded one level due to serious indirectness related to patient population.

^cDowngraded two levels due to very serious imprecision with very wide confidence intervals.

Summary of findings 7. Oral nutritional supplements compared to multivitamin and mineral supplement for treatment of bladder cancer by radical cystectomy

Oral nutritional supplements compared to multivitamin and mineral supplement for treatment of bladder cancer by radical cystectomy

Patient or population: treatment of bladder cancer by radical cystectomy

Setting: Vanderbilt Hospital, USA

Intervention: oral nutritional supplements

Comparison: multivitamin and mineral supplement

Outcomes	Nº of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with multivitamin and mineral supplement	Risk difference with oral nutritional supplements
Complications Follow-up: 30 days	61 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	RR 0.73 (0.47 to 1.13)	Study population 500 per 1000	 135 fewer per 1000 (265 fewer to 65 more)
Length of hospital stay	61 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	—	The mean length of hospital stay was 8.9 days	MD 0.3 days fewer (3.64 fewer to 3.04 more)
Mortality Follow-up: 30 days	61 (1 RCT)	⊕⊕⊕⊖ Low ^{a,b}	RR 0.97 (0.06 to 14.78)	Study population 33 per 1000	 1 fewer per 1000 (31 fewer to 459 more)

***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; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence

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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.

^aDowngraded one level for study limitations (unclear selection, performance and detection bias).

^bDowngraded one level due to imprecision and wide confidence intervals.

BACKGROUND

Description of the condition

The worldwide incidence of bladder cancer is reported to be 5.3 per 100,000 people (age-standardised rate), and the condition is significantly more prevalent in men (9.0 per 100,000) than in women (2.2 per 100,000) (GLOBOCAN 2012).

When bladder cancer is diagnosed, the majority of people (70% to 75%) have superficial bladder cancer where malignant changes are located on the bladder surface (the urothelium) and limited by the lamina propria (fibrous layer beneath the urothelium) (de Braud 2002; Tobias 2010). The standard treatment for this is transurethral resection of bladder tumour, which involves the removal of the abnormal tissue endoscopically; this may be followed by the instillation of a chemotherapy agent directly into the bladder to reduce the recurrence rate. The most common histological subtype is transitional cell carcinoma. People then require regular follow-up inspections of the bladder by cystoscopy to detect any recurrence of the tumour.

Where bladder cancer has invaded beyond the lamina propria and into the bladder wall muscle layers, it is termed muscle-invasive bladder cancer. This may be found at initial presentation or may result from cancer progression in about 10% to 25% of cases previously diagnosed with non-invasive bladder cancer (de Braud 2002). The bladder tumour tissue can invade into muscle and in more extensive cases can also infiltrate into adjacent organs such as the prostate, uterus and vagina, or become fixed to the pelvic side wall. Invasive bladder cancer is associated with a greatly increased mortality rate in comparison to non-invasive bladder cancer. One of the management options is surgery, which in advanced cases is combined with neoadjuvant chemotherapy. The surgical operation is termed a radical (or total) cystectomy (RC); RC may also be indicated for people who have widespread non-muscle invasive, but high-grade tumour associated with carcinoma-in-situ.

RC is a major surgical procedure consisting of the removal of the bladder, together with the prostate and seminal vesicles in men, or the bladder and urethra, together with the anterior vaginal wall and uterus in women. Additionally, the pelvic lymph nodes are removed (pelvic lymphadenectomy). In the absence of the bladder, urine must be surgically diverted; this is most commonly achieved using a small loop of ileum (small bowel) into which the ureters are connected and then opens onto the abdominal wall as a stoma (a urostomy) with urine collected in a stoma bag. It may be possible to reconstruct a neobladder using a segment from the small or large bowel (bladder reconstruction) so that urine can be voided through the usual route via the urethra if this is retained, or via a catheterisable stoma made from the appendix or small bowel which acts as a channel between the neobladder and skin surface. An alternative treatment is the implanting of the ureters into the sigmoid colon (large bowel) or the rectum.

Although the mortality rate for cystectomy is now relatively low (1.5% in Shabsigh 2009 and 3% in Stein 2003), complications have been identified in up to 64% of people, including 13% major complications within 90 days of surgery (Shabsigh 2009). Possible complications include wound infections, intestinal obstruction, haemorrhage, cardiopulmonary complications and rectal injury.

Bladder cancer predominately occurs in older people. In the UK from 2005 to 2007, RC was undertaken in 4070 people with a mean age of 67 years (median age 68 years) with many over 70 years (SWPHO 2011). People with bladder cancer may have significant nutritional issues, older people have an increased likelihood of malnutrition compared to younger adults, and this may be due to the presence of comorbidities, poorer access to food, decreased appetite and food intake. When people have cancer, additional causes of malnutrition and weight loss can include inadequate dietary intake due to tumour-induced anorexia; catabolic tumour effects; abnormal metabolism of nutrients; reduced food intake secondary to the adverse effects of radiotherapy or chemotherapy; and diminished intake due to pain, anxiety or depression (Henry 2011). Sarcopenia, which is a loss of muscle mass, is now being considered as a possible factor contributing to the risk of complications and survival in RC (Smith 2014).

Nutritional requirements are liable to increase secondary to the disease process and surgical interventions. In one study of body composition in 11 people undergoing RC where nutritional support was not provided, there was evidence of protein depletion at baseline. Significant loss of protein was noted in almost half of the group 14 days after the procedure and protein loss was associated with postoperative complications; total body protein was not fully regained six months after RC (Mathur 2007). In a separate study, people who were given dextrose infusions post-RC were calculated to have mean nitrogen losses of 6.6 g per day, which was significantly higher than among people who were tube fed into the jejunum (Daly 1987).

Nutritional status is an important factor in determining postoperative outcomes in RC (Villa 2017), and several methods have been used to evaluate the incidence of malnutrition in people with bladder cancer. A 'Nutrition Risk Screening 2002' tool (combining assessment of weight loss, decreased food intake and disease severity) was used in a prospective assessment, 24% of people with urological cancers (including 40% with bladder cancer) had a high nutrition risk score (Karl 2009). In a survey of 277 urologists in the UK, the proportion of inadequately nourished people admitted for RC was estimated to be 23% (Barrass 2006). Although there is a high incidence of obesity in people undergoing RC in the US (26%) (Shabsigh 2009), the presence of excess weight may mask evidence of significant weight loss; therefore, better assessment techniques are required which will identify malnutrition in populations with a high incidence of people who are overweight or obese.

Current guidelines recommend the use of nutritional screening for people in hospitals for the purpose of identifying those at risk of malnutrition (Kondrup 2003; Mueller 2011; NICE 2006; Weimann 2017). The identification of people who are malnourished or at risk of malnutrition should be linked to further nutrition assessment, and the implementation of an appropriate nutrition care plan, which may include nutrition support.

Other Cochrane Reviews have examined perioperative feeding issues and found mixed results. In gastrointestinal surgery, there were reduced complications postoperatively with immuno-enhancing nutrition (Burden 2012a), and in women with ovarian cancer in the perioperative period there was very limited evidence to direct clinical practice (Billson 2013). There has also been a systematic review in people after radiotherapy, which included studies on participants after surgical intervention for bladder

cancer (Lawrie 2018). However, this review examined late effects after treatment.

Description of the intervention

The role of nutrition in the perioperative treatment of bladder cancer by RC encompasses several themes, including the identification of malnutrition in people undergoing RC and the provision of appropriate nutrition support; the use of preoperative nutrition as part of enhanced recovery or Enhanced Recovery After Surgery (ERAS) programmes; the appropriate timing and source of nutrition introduced postoperatively; and the use of nutrition support to manage adverse effects resulting from surgery involving the gastrointestinal tract.

In this context, nutrition support is the supply of nutrients to people other than the standard provision of nourishment, with the intention to improve or maintain nutrient intake. Nutrition support may be provided as supplementary food or drink, fortified food, oral nutrition supplements, formulations that are given by tube into the gastrointestinal tract (enteral feeds) or feeds which are given by infusion directly into a vein referred to as parenteral nutrition (PN). Nutrition support may compensate in part or in full for inadequate food consumption. In addition, nutrition support may be given at any stage during the perioperative period during which RC is undertaken with the intention to prevent or treat malnutrition. It is important that the risk of adverse effects associated with the provision of nutrition support is considered. Risks associated with nutrition support interventions could range from minor effects such as nausea to life-threatening effects including PN catheter-related bloodstream infections.

How the intervention might work

Malnutrition has been linked to complications following RC. Thirteen out of 33 (39%) people undergoing RC in one US series were described as malnourished. Malnutrition was associated with significantly increased perioperative morbidity, mortality and days in intensive care, compared with well-nourished counterparts (Mohler 1987). In a more recent report of 538 people undergoing RC, 19% met the study criteria for nutritional deficiency and the results showed that they were at a greater risk of death within 90 days of the surgery (hazard ratio 2.91, 95% confidence interval (CI) 1.36 to 6.23; $P \leq 0.01$) and less likely to be alive three years later, compared to those judged to be well nourished (Gregg 2011).

When the complexity of case mix and risk factors for RC were examined in a prospective study of 2538 people, preoperative factors associated with mortality and prolonged length of hospital stay were old age, American Association of Anesthetists (ASA) score of 3 or more, dependent functional status and low serum albumin. While it was noted that some factors could not be altered, it was felt that preoperative nutritional supplementation may be beneficial. Since there was significant weight loss greater than 10% in the previous six months in 5.4% of people and which was associated with increased mortality at 30 days (odds ratio (OR) 2.7, 95% CI 1.1 to 6.4) and at 90 days (OR 2.9, 95% CI 1.5 to 5.4), this factor may also be amenable to preoperative nutrition intervention (Hollenbeck 2006).

The use of nutrition supplements preoperatively for carbohydrate loading may be indicated for people undergoing RC in ERAS programmes. The role of ERAS protocols in RC, including the use of

carbohydrate drinks two hours prior to surgery, has been reviewed (Melnyk 2011). These programmes have the purpose of facilitating recovery from surgery by adherence to standard protocols with the aim of reducing postoperative complications and hospital stay.

Postoperatively, there is no current consensus on the appropriate provision of nutrition. In a UK survey, the majority (60%) of urologists employed a traditional strategy of bowel rest and feeding orally after bowel recovery; a minority used PN (18.5%) or enteral nutrition (6.5%) routinely, although a larger proportion (29%) considered that enteral nutrition was the "optimal" feeding regimen (Barrass 2006).

Postcystectomy, PN is often used because of the delayed return of bowel function resulting from postoperative ileus. This is one of the most frequent postoperative complications resulting in increased length of hospital stay, with a documented incidence of 10% to 20% (Hollenbeck 2006). In a review of complications occurring within 90 days post-RC in 1142 people, gastrointestinal complications were the most frequently reported (29%) with ileus as the most common problem; this was defined as any inability to tolerate solid food five days after surgery; the need for a nasogastric tube; or need to stop oral intake due to abdominal distension, nausea or vomiting.

In early studies, the use of PN postoperatively was associated with a significantly reduced length of hospital stay compared with people only given 5% dextrose. This may have been due to a decreased rate in the return of postoperative physical activity in people on dextrose (Askanazi 1986). People who were considered to be malnourished appeared to benefit from perioperative PN, had fewer complications and a shorter hospital stay than the nutritionally 'at risk' control group. However, there were small numbers of malnourished people in the study (Chin 1983). A meta-analysis in 2001 reviewed 27 randomised controlled trials (RCT) and concluded that there may be a reduction in complication rates but not death rates for people receiving PN (Heyland 2001).

More recently, a variety of nutrition strategies have been employed on multimodal programmes for people undergoing RC (Azhar 2016; Maffezzini 2006). When a multimodal programme was introduced for people undergoing RC, the use of early oral nutrition was one of the factors associated with reduced postoperative pain, more rapid mobilisation and a shorter time to defecation compared to PN (Brodner 2001). However, adherence to all aspects of multimodal programmes has been questioned (Rattray 2018). There is also an interest within oncology surgery for prehabilitation where nutrition can form part of multimodal treatments preoperatively (Jensen 2018). Some studies have shown that the use of preoperative oral supplementation improves some clinical outcomes in participants with cancer (Burden 2017). An alternative programme included the early introduction of liquids and introduction of a regular diet on day four postoperatively, irrespective of flatus or bowel movements; this was only delayed if the patient had nausea or vomiting. Mean time to achieving a clear liquid diet intake was two days and to regular diet was 4.2 days with mean discharge at 5.1 days. Surgical techniques employed to minimise the manipulation and dissection of the small bowel plus limited incisions may have reduced the chance of postoperative bowel oedema and ileus. However, the authors indicated that early institution of an oral diet has had the greatest impact on early discharge (Pruthi 2003). There was a significantly reduced hospital stay in Bristol (UK), where clear fluids were introduced in recovery and light diet was permitted

from day two postoperatively, or nasogastric feeding from day five if foods were not tolerated (Arumainayagam 2008).

Why it is important to do this review

Bladder cancer is associated with significant morbidity and mortality rates. Malnutrition may be associated with a poorer outcome but the evidence base for nutritional intervention is limited. It was noted that the evidence related to benefits of nutrition support in people undergoing RC was equivocal and that randomised trials are needed to assess the effect of perioperative nutrition in this patient group (Thurairaja 2005). Results from questionnaires completed by urologists performing cystectomies in the UK indicated a diversity in practice, not all based on clinical guidelines (Barrass 2006). It has been suggested that there is a need to demonstrate the best indices of preoperative nutritional status, and whether nutritional intervention can alter the poorer prognosis for people who are nutritionally deficient undergoing RC (Gregg 2011). Current guidelines for nutrition in surgery support the integration of nutritional support in to perioperative management for patients (Weimann 2017). In undertaking this review using Cochrane guidelines to investigate the use of perioperative nutrition in this group we aimed to produce a methodologically rigorous systematic review including a comprehensive literature search, with a focus on patient-important outcomes and rating of the quality of evidence using GRADE. We expect that this review will contribute to raising awareness of the need to consider nutritional issues as part of the supportive care for people undergoing RC.

OBJECTIVES

To assess the effects of perioperative nutrition in participants undergoing radical cystectomy for the treatment of bladder cancer.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) and quasi-RCTs.

Types of participants

Adults undergoing RC for bladder cancer. Where trials also included participants undergoing other types of procedures, we only included studies where more than 95% of participants were undergoing a surgical treatment of cancer and where at least 65% of the participants were undergoing RC. The diagnosis and definition of bladder cancer is described in current guidelines (NICE 2015).

Types of interventions

Nutritional interventions were provided at any stage in the perioperative period during which RC was undertaken as a treatment for bladder cancer. Nutritional interventions could have been one or more of the following: additional food or drink, fortified foods, oral supplements, and enteral or parenteral feeds. Nutritional products could have been supplementary to the usual food and drink or could have been the sole source of nourishment. Trials may have examined the provision of nutrition support in comparison with not providing nutrition support or may have compared alternative types of nutrition support. Studies where a nutritional intervention was only one factor in a package of care being evaluated were excluded.

Comparisons which included any nutritional interventions versus standard or usual care.

If a trial included multiple arms, we included any arm that met the inclusion criteria in the review.

Minimum duration of intervention and follow-up

We defined trial duration according to the number of days over which the intervention had been given and included trials in the analysis where the interventions had been given for any time period. We included follow-up data on the specified outcomes up to 90 days postoperatively. When only 30-day data were available, we reported those figures.

Types of outcome measures

Primary outcomes

- Complications up to 90 days after surgery (e.g. sepsis, wound breakdown, paralytic ileus or infections).
- Length of hospital stay.

For length of hospital stay we considered a difference of one day as clinically important.

Secondary outcomes

- Mortality reported up to 90 days after surgery.

Search methods for identification of studies

We performed a comprehensive search for studies, with no restrictions based on language of publication or publication status.

Electronic searches

We searched the following electronic databases to 22 June 2018.

- Evidence Based Medicine Reviews (via Ovid; from 1991; for the search strategy, see Appendix 1).
- MEDLINE (via Ovid; from 1946; see Appendix 2).
- Embase (via Ovid; from 1974; see Appendix 3).
- AMED (via Ovid; from 1985; see Appendix 4).
- CINAHL (via EBSCO; from 1937; see Appendix 5).

We searched the following trials registers to June 2018.

- metaRegister of Controlled Trials (mRCT; www.controlled-trials.com/mrct/active; see Appendix 6).
- National Cancer Institute (NCI; www.cancer.gov/clinicaltrials; see Appendix 7).
- ClinicalTrials.gov (www.clinicaltrials.gov; see Appendix 8).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who-int/ictip; see Appendix 9).

We searched meeting abstracts through the following websites to June 2017.

- Zetoc (zetoc.mimas.ac.uk; see Appendix 10).
- OCLC WorldCat Dissertations and Theses (WorldCatDissertations; see Appendix 11).

We carried out translations when needed.

Searching other resources

Where we identified ongoing trials, we attempted to contact principal investigators to request relevant data. The citation lists of included studies were handsearched to identify any further relevant trials. We handsearched reference lists of relevant systematic reviews.

Data collection and analysis

Selection of studies

Groups of two review authors (from HAB, SB and KO) independently assessed the titles and abstracts retrieved by the searches to determine relevance and eligibility. We obtained the full-text article where there was insufficient information in the abstract and title. Two review authors (HAB, SB) working independently or one of these authors and a clinically trained translator, reviewed relevant records in full text, mapped records to studies and classified studies as included or excluded studies in accordance with the criteria in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Diversity of opinion was resolved by discussion. Reasons for exclusion of studies were documented. In studies where there were multiple reports of the same cohort, all the manuscripts reporting the outcomes were included. Where the same outcomes were reported, we included the latest study with the longest follow-up.

Data extraction and management

Two review authors (HAB and SB) independently undertook data extraction using a piloted and modified data collection form. They resolved discrepancies between themselves or, where translation was required, one of these review authors worked with a translator. We extracted the following information.

- Year of publication, country of origin and source of funding.
- Participant details, number of participants, age, inclusion and exclusion criteria.
- Cancer diagnosis, including staging if indicated, type of surgery used.
- Details of nutritional intervention (including type of food, drink, formulation, route of intervention, duration of intervention and quantity delivered).
- Details of primary and secondary outcomes, including the time points when these were collected and reported.

For dichotomous outcomes, we extracted the number of participants in each treatment arm who experienced the outcome of interest, and the number of participants assessed at endpoint.

For continuous outcomes, we extracted the final value and standard deviation of the outcome of interest, and the number of participants assessed at endpoint in each treatment arm at the end of follow-up.

We extracted both unadjusted and adjusted statistics, if reported.

Where possible, we extracted data relevant to an intention-to-treat analysis, in which participants were analysed in the groups to which they were assigned.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies using Cochrane's 'Risk of bias' tool (Higgins 2011). This included assessment of the following.

- Selection bias:
 - random sequence generation;
 - allocation concealment.
- Performance bias:
 - blinding of participants and personnel (patients and treatment providers), we evaluated the risk of bias separately for each outcome according to whether susceptible to performance bias.
- Detection bias:
 - blinding of outcome assessment, we evaluated the risk of bias separately for each outcome, and grouped outcomes according to whether measured subjectively or objectively.
- Attrition bias:
 - incomplete outcome data. We assessed attrition bias (incomplete outcome data) and reporting bias (selective reporting) on a per-outcome basis.
- Reporting bias:
 - selective reporting.
- Other possible sources of bias.

Two review authors (HAB, SB) independently applied the 'Risk of bias' tool and resolved differences by discussion. Results of the assessment were summarised in the 'Risk of bias' summary (Figure 1) and 'Risk of bias' graph (Figure 2).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias): Objective outcomes	Blinding of participants and personnel (performance bias): Subjective outcomes	Blinding of outcome assessment (detection bias): Complications	Blinding of outcome assessment (detection bias): Length of hospital stay	Blinding of outcome assessment (detection bias): Mortality	Incomplete outcome data (attrition bias): Complications	Incomplete outcome data (attrition bias): Length of hospital stay	Incomplete outcome data (attrition bias): Mortality	Selective reporting (reporting bias)	Other bias
Bonau 1984	?	?	+	?	?	?	+	?	?	+	?	+
Daly 1982	?	?	+	?	?	+	+	+	+	+	?	+
Deibert 2016	+	?	+	?	?	+	+	+	+	+	+	+
Hamilton-Reeves 2016	+	+	+	+	+	+	+	+	+	+	+	+
Hensle 1978	-	-	+	?	?	+	+	+	+	+	?	+
Ritch 2018	?	?	+	?	?	+	+	+	+	+	+	+
Roth 2013	+	?	+	?	+	+	+	+	+	+	?	+
Rovera 1989	?	?	+	?	?	+	+	+	?	+	?	+

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

For selection bias (random sequence generation and allocation concealment) and reporting bias (selective reporting), we evaluated risk of bias at a trial level.

For performance bias (blinding of participants and personnel) and detection bias (blinding of outcome assessment), we evaluated the risk of bias separately for each outcome, and grouped outcomes according to whether they were measured subjectively or objectively.

We defined the following endpoints as subjective outcomes for performance bias (blinding of participants and personnel):

- complications;
- length of hospital stay.

We defined the following endpoint as an objective outcome for performance bias (blinding of participants and personnel):

- mortality.

The endpoint classed as subjective for detection bias (blinding of outcome assessment) was:

- complications.

The endpoints defined as objective for detection bias (blinding of outcome assessment) were:

- mortality;
- length of hospital stay.

Attrition bias (incomplete outcome data) was assessed on an outcome-specific basis.

Measures of treatment effect

For measures of the effect of treatment: for dichotomous outcomes, we used the risk ratio (RR) with 95% confidence interval (CI), and for continuous outcomes, the mean difference (MD) with 95% CI.

Unit of analysis issues

We planned to consider trials that were cluster-randomised on an individual basis to determine whether they should be included with unit of analysis issues examined by two review authors (Higgins 2011), but none were included.

If there were multiple interventions in the same study, we planned to combine these and compare to the control if appropriate, but this issue was not relevant in the included studies.

Dealing with missing data

In studies with missing data, we planned to contact the study authors to seek relevant information; however, this was not practical due to the historic nature of several of the studies. No missing outcome data was imputed, participants were analysed according to the intention-to-treat principle.

Assessment of heterogeneity

We assessed heterogeneity between studies by visual inspection of forest plots, with the presence of heterogeneity being indicated by poor overlap between the CIs of individual studies, depicted by horizontal lines. The percent of heterogeneity between trials which could not be ascribed to sampling variation (Higgins 2003), was assessed by a formal statistical test of the significance of the heterogeneity using I^2 statistic (Deeks 2001). Subgroup analyses were planned to attempt to determine possible reasons for any identified heterogeneity; however, this was not appropriate with the included studies.

Assessment of reporting biases

We searched multiple sources (see [Search methods for identification of studies](#)). Consideration was made about whether trials were undertaken and reported according to the trial protocol if this was available. It was planned that publication bias would be assessed using a funnel plot as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Sterne 2011); however, an insufficient number of trials were identified.

Data synthesis

The results of clinically similar studies were pooled in meta-analyses. For the meta-analysis of the quantitative data, we used the random-effects model. Statistical analyses were conducted according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For dichotomous outcomes, we used the Mantel-Haenszel method and for continuous outcomes the inverse variance method. Review Manager software was used to perform analyses (Review Manager 2014). If there was significant heterogeneity between the studies, meta-analysis would not have been undertaken but possible causes of heterogeneity would have been examined. Clinically heterogeneous trials were presented individually in a descriptive analysis.

Subgroup analysis and investigation of heterogeneity

There was a lack of suitable data, therefore subgroup analyses were not undertaken. The planned subgroup analyses were:

- malnourished participants versus non-malnourished participants;
- type of nutrition intervention;
- comparing trials conducted before 1990 versus subsequently (since then there have been significant developments in artificial feeding and nutrition support).

In the interpretation of any heterogeneity, we considered baseline characteristics including factors of age (less than 70 years and 70 years and older), cancer staging, type of nutrition intervention

(oral, enteral, parenteral) and length of follow-up (one month, three months).

Sensitivity analysis

If six or more studies had been suitable for meta-analysis in this review, we planned to conduct sensitivity analyses by repeating the analysis with the following adjustments: exclusion of trials with unclear or incomplete reporting of complications and trials with incomplete follow-up. Additionally, sensitivity analysis were planned excluding studies judged 'high' or 'unclear' risk of bias.

'Summary of findings' tables

The overall certainty of the evidence for each outcome was rated according to the GRADE approach taking into account five criteria related both to internal validity (risk of bias, inconsistency, imprecision, publication bias) and external validity (directness of results) (Guyatt 2008). For each comparison, two review authors (SB, HB) independently rated the quality of the evidence for each outcome as 'high', 'moderate', 'low', or 'very low', and resolved discrepancies by discussion. We used GRADEpro GDT to prepare summaries of the evidence for the primary outcomes in 'Summary of findings' tables for each comparison, in accordance with Cochrane guidance (Schünemann 2011).

RESULTS

Description of studies

See [Characteristics of included studies](#), [Characteristics of excluded studies](#), and [Characteristics of ongoing studies](#) table.

Results of the search

See [Figure 3](#). The searches and updated searches run on the electronic databases to 22 February 2019 identified 5514 titles; after scanning titles and reviewing abstracts, we obtained 16 full reports describing relevant studies plus a further study in a conference abstract and one study from an ongoing trial. Translation of four reports was undertaken. Of the 18 studies, eight met the inclusion criteria for this review and 10 studies were excluded. There were no quasi-RCTs.

Figure 3. Study flow diagram.

Included studies

See [Characteristics of included studies](#) table.

In the eight studies which met the inclusion criteria there were 500 trial participants, all were undergoing RC and all studies were conducted in a hospital setting (Bonau 1984; Daly 1982; Deibert 2016; Hamilton-Reeves 2016; Hensle 1978; Ritch 2018; Roth 2013; Rovera 1989). In the studies that reported gender, there were 341 men and 82 women (Bonau 1984; Deibert 2016; Hamilton-Reeves 2016; Ritch 2018; Roth 2013; Rovera 1989); two studies recruited only men (Bonau 1984; Hamilton-Reeves 2016). Six studies described the age of the participants who had group mean or median ages between 61 and 69 years or were included in a range of ages from 30 to 84 years (Bonau 1984; Daly 1982; Hamilton-Reeves 2016; Ritch 2018; Roth 2013; Rovera 1989). One study received supported from Abbott Laboratories (Bonau 1984); one study from an educational grant from McGaw Laboratories (Hensle 1978); one study from the American Cancer Society, Nestle Healthcare and travel funding (Hamilton-Reeves 2016); one study from Vanderbilt CTSA, NIH National Centre and Abbott Nutrition Award (Ritch 2018); two studies received no funding (Deibert 2016; Roth 2013); and two studies provided no disclosure of funding sources (Daly 1982; Rovera 1989).

Two included studies conducted in the USA (134 participants) evaluated amino acid solutions with and without dextrose compared to dextrose solution in the postoperative management of people following RC (Daly 1982; Hensle 1978). Daly 1982 randomised 93 participants into three arms, although only two arms are included in the analysis with 60 participants comparing

amino acid solution plus dextrose to dextrose solution as the control. One study (19 participants) in the USA compared two different branched chain amino acid solutions to dextrose solution (Bonau 1984). There were three arms although only two arms were suitable to be included in this review including 10 participants (Bonau 1984). One study conducted in Italy (28 participants) investigated preoperative oral nutritional support and postoperative PN compared to a control group that only received postoperative PN (Rovera 1989). One study including 157 participants conducted in Switzerland also investigated PN and evaluated PN postoperatively compared to oral diet (Roth 2013). One study with 29 participants compared immuno-enhancing nutrition supplements and standard oral nutritional supplements given for five days before and five days after RC surgery (Hamilton-Reeves 2016). One study including 102 participants compared early feeding with clear liquid on day one after surgery followed by access to full oral diet on day two after surgery, in comparison to standard postoperative management (Deibert 2016). One study including 61 participants compared oral nutritional supplements administered three to four weeks preoperatively and four weeks postoperatively to oral multivitamin and mineral supplement (Ritch 2018).

Excluded studies

See [Characteristics of excluded studies](#) table.

We excluded 10 studies from the review (Brodner 2001; Daly 1987; de Vries 2012; Hensle 1985; Karl 2009; Malossini 1987; Mangano 1993; McArdle 1986; Olbert 2009; Solomon 1978). Six studies did not randomise participants, two studies did not include a nutritional

intervention, one study had insufficient RC participants included and one study did not fully meet the inclusion criteria.

Ongoing studies

See [Characteristics of ongoing studies](#) table.

We classified three studies as ongoing studies ([NCT02238886](#); [NCT03147586](#); [NCT03204266](#)). One of these studies is being undertaken in the USA ([NCT03204266](#)), one in Denmark ([NCT02238886](#)), and one in Egypt ([NCT03147586](#)).

Risk of bias in included studies

The risk of bias in the included studies is summarised in [Figure 1](#) and displayed graphically in [Figure 2](#).

Allocation

Selection bias was assessed in the form of the risk of bias domains of random sequence generation and allocation concealment.

Random sequence generation

In relation to random sequence generation, there was a low risk of bias in three studies as randomisation was undertaken by a statistician in one study ([Hamilton-Reeves 2016](#)), by a computer in one study ([Roth 2013](#)), and described in the protocol in one study ([Deibert 2016](#)). In four studies, the risk of bias was unclear ([Bonau 1984](#); [Daly 1982](#); [Ritch 2018](#); [Rovera 1989](#)). There was a high risk of selection bias in one study as primary physicians changed some group allocations so not all participants received the treatment they were assigned from the randomisation process ([Hensle 1978](#)).

Allocation concealment

In one study, there was a low risk of bias in relation to allocation concealment ([Hamilton-Reeves 2016](#)). In six studies, the information on allocation to groups was limited, so level of bias was unclear ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)). In one study, the risk of bias was high as the allocation was not concealed ([Hensle 1978](#)).

Blinding

Blinding of participants and personnel

For objective outcomes (mortality), eight studies had a low risk of bias ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)).

For subjective outcomes (complications and length of hospital stay), one study had a low risk of bias ([Hamilton-Reeves 2016](#)). The risk of bias was unclear for seven studies ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)).

Blinding of outcome assessment

Outcome – complications: two studies had a low risk of bias ([Hamilton-Reeves 2016](#); [Roth 2013](#)), and six studies had an unclear risk of bias ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Rovera 1989](#)).

Outcome – length of hospital stay: eight studies had a low risk of bias ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)).

Outcome – mortality: eight studies had a low risk of bias ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)).

Incomplete outcome data

Outcome – complications: one study had an unclear risk of bias ([Bonau 1984](#)); seven studies had a low risk of bias ([Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)).

Outcome – length of hospital stay: six studies had a low risk of bias ([Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)), and two studies had an unclear risk of bias ([Bonau 1984](#); [Rovera 1989](#)).

Outcome – mortality: eight studies had a low risk of bias ([Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#)).

Selective reporting

Three studies had a low risk of bias ([Deibert 2016](#); [Hamilton-Reeves 2016](#); [Ritch 2018](#)), and five studies had an unclear level of reporting bias where study protocols were not located although all outcomes in the methods section of the studies were reported in the results ([Bonau 1984](#); [Daly 1982](#); [Hensle 1978](#); [Roth 2013](#); [Rovera 1989](#)).

Other potential sources of bias

Eight studies were at low risk for other sources of bias [Bonau 1984](#); [Daly 1982](#); [Deibert 2016](#); [Hamilton-Reeves 2016](#); [Hensle 1978](#); [Ritch 2018](#); [Roth 2013](#); [Rovera 1989](#).

A description of the interventions are shown in [Table 1](#) and baseline characteristics are shown in [Table 2](#).

Effects of interventions

See: [Summary of findings for the main comparison](#) Postoperative parenteral nutrition compared to oral nutrition alone for the treatment of bladder cancer by radical cystectomy; [Summary of findings 2](#) Immunonutrition compared to standard nutritional supplements for the treatment of bladder cancer by radical cystectomy; [Summary of findings 3](#) Preoperative oral nutritional support compared to normal diet for the treatment of bladder cancer by radical cystectomy; [Summary of findings 4](#) Early postoperative feeding compared to standard management for the treatment of bladder cancer by radical cystectomy; [Summary of findings 5](#) Amino acid solution, alone or in combination with dextrose compared to dextrose solution for the treatment of bladder cancer by radical cystectomy; [Summary of findings 6](#) Branch chain amino acids compared to dextrose for the treatment of bladder cancer by radical cystectomy; [Summary of findings 7](#) Oral nutritional supplements compared to multivitamin and mineral supplement for treatment of bladder cancer by radical cystectomy

Comparison 1: postoperative parenteral nutrition compared to oral nutrition

We found one study, including 157 participants (74 PN, 83 control) that compared postoperative PN to oral nutrition alone ([Roth 2013](#)). See [Summary of findings for the main comparison](#).

Primary outcomes

Complications up to 90 days after surgery

Based on one study with 157 participants, PN may have increased postoperative complications within 30 days (RR 1.40, 95% CI 1.07 to 1.82; low-quality evidence; [Analysis 1.1](#)). We downgraded the quality of evidence for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious imprecision. Assuming a baseline risk of postoperative complications of 49%, this corresponded to 198 more complications per 1000 participants (95% CI 35 more to 405 more).

This study was discontinued prematurely due to more complications occurring in the PN group.

Length of hospital stay

Length of hospital stay may have been similar (MD 0.5 days more, CI not reported; low-quality evidence). We downgraded the quality of evidence for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious imprecision. Length of hospital stay was recorded as a mean of 16 days in the PN group and in the oral diet group was a mean of 15.5 days.

Secondary outcomes

Mortality

We were very uncertain of the effect of PN compared to oral diet on postoperative mortality rates (RR 1.12, 95% CI 0.07 to 17.62; very low-quality evidence; [Analysis 1.2](#)). We downgraded the quality of evidence for serious study limitations (unclear risk of selection, performance and selective reporting bias) and very serious imprecision. Assuming a baseline risk of postoperative mortality of 1%, PN may have resulted in 1 more death per 1000 participants (95% CI 11 fewer to 200 more).

Comparison 2: immuno-enhancing nutrition compared to standard oral nutritional supplements

We found one study including 29 participants that compared specialised immuno-enhancing oral supplements to standard oral nutritional supplements given three times per day for five days before and five days after RC surgery ([Hamilton-Reeves 2016](#)). See [Summary of findings 2](#).

Primary outcomes

Complications up to 90 days after surgery

Immuno-enhancing nutrition may improve rates of 90-day postoperative complications compared to usual diet (RR 0.31, 95% CI 0.08 to 1.23; low-quality evidence; [Analysis 2.1](#)). We downgraded the quality of evidence for very serious imprecision. Assuming a baseline risk of postoperative complications of 46%, immuno-enhancing nutrition may have resulted in 322 fewer occurrences per 1000 participants (95% CI 429 fewer to 107 more).

We also found data on 30-day complication rates, which we chose to report given that it was the most prevalently reported time-frame for the outcome of complications for other comparisons. Immuno-enhancing nutrition versus usual care may have had little or no effect on rates of 30-day postoperative complications (RR 0.97, 95% CI 0.62 to 1.53; low-quality evidence; [Analysis 2.2](#)). We downgraded the quality of evidence for imprecision. Assuming a baseline risk of

postoperative complications of 66%, immuno-enhancing nutrition would have resulted in 20 fewer occurrences per 1000 participants (95% CI 253 fewer to 353 more).

Length of hospital stay

Length of hospital stay may have been similar (MD 0.20 days fewer, 95% CI 1.69 fewer to 2.09 more; low-quality evidence; [Analysis 2.3](#)). We downgraded the quality of evidence for very serious imprecision.

Secondary outcomes

Mortality

Immuno-enhancing nutrition compared to standard may have had little or no effect on mortality rates (RR approximately 1, CI not reported; low-quality evidence). There were no deaths reported in the period up to 90 days postoperatively. We downgraded the quality of evidence for assumed very serious imprecision. No absolute effect size estimates for the CIs could be generated.

Comparison 3: preoperative oral nutritional support compared to normal diet

We found one study including 28 participants that compared preoperative oral nutritional support to normal diet ([Rovera 1989](#)). Both groups also had postoperative PN. See [Summary of findings 3](#).

Primary outcomes

Complications up to 90 days after surgery

We were very uncertain if preoperative oral supplements reduced postoperative complications ([Analysis 3.1](#)). We downgraded for serious study limitations (unclear risk of selection, performance, attrition and selective reporting bias) and very serious imprecision. Assuming a baseline risk of postoperative complications of 18%, preoperative nutrition would have resulted in 21 fewer occurrences per 1000 participants (95% CI 154 fewer to 658 more).

Length of hospital stay

The study did not report length of hospital stay.

Secondary outcomes

Mortality

We were uncertain whether preoperative oral nutrition compared to standard care had an effect on mortality rates (RR approximately 1, CI not reported; very low-quality evidence). We downgraded the quality of evidence for study limitations and too few events to reliably evaluate this outcome. There were no deaths reported in either group.

Comparison 4: early postoperative feeding compared to standard postoperative management

We found one study including 102 participants that compared the provision of clear fluids on the first day after surgery and access to a full diet on the second day following RC compared with standard postoperative care where oral intake was delayed until either flatus or a bowel movement had occurred ([Deibert 2016](#)). Follow-up was reported for a period of 90 days after surgery.

See [Summary of findings 4](#). All data for this comparison were obtained from the published report, the authors provided us with the study protocol.

Primary outcomes

Complications up to 90 days after surgery

Early postoperative feeding compared to standard care may have had little or no effect on postoperative complications (RR 1.14, 95% CI 0.85 to 1.53; very low-quality evidence; [Analysis 4.1](#)). We downgraded the quality of evidence for study limitations and very serious imprecision. Assuming a baseline risk of postoperative complications of 59%, early postoperative feeding would have resulted in 83 more occurrences per 1000 participants (95% CI 89 fewer to 316 more).

Length of hospital stay

Early postoperative feeding compared to standard care may have had little or no effect on length of hospital stay (MD 0.95 days fewer, CI not reported; low-quality evidence). We downgraded the quality of evidence for study limitations and the study was underpowered to demonstrate a clinically important difference of one day in length of hospital stay.

Secondary outcomes

Mortality

Early postoperative feeding compared to standard care may have had little or no effect on postoperative mortality rates (RR 0.52, 95% CI 0.10 to 2.71; low-quality evidence; [Analysis 4.2](#)). We downgraded the quality of evidence for study limitations and imprecision.

Assuming a baseline risk of postoperative mortality of 3.8%, early feeding would have resulted in 19 fewer occurrences per 1000 participants (95% CI 35 fewer to 72 more).

Comparison 5: amino acid solution with dextrose compared to dextrose solution alone

We found two studies including 104 participants that compared an amino acid solution alone or in combination with dextrose, to dextrose solution ([Daly 1982](#); [Hensle 1978](#)). See [Summary of findings 5](#).

Primary outcomes

Complications up to 90 days after surgery

Two studies including 104 participants reported complications ([Daly 1982](#); [Hensle 1978](#)).

We were uncertain if amino acid solution alone or in combination with dextrose solution had any effect on postoperative complications (RR 0.77, 95% CI 0.32 to 1.82; $I^2 = 13\%$; very low-quality evidence; [Analysis 5.1](#); [Figure 4](#)). We downgraded the quality of evidence for study limitations, indirectness as the study used historical methods and imprecision. Assuming a baseline risk of postoperative complications of 20%, amino acid solution alone or in combination with dextrose solution would have resulted in 46 fewer occurrences per 1000 participants (95% CI 136 fewer to 164 more).

Figure 4. Forest plot of comparison 5: amino acid and dextrose compared to dextrose, outcome: 5.1 complications.

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias): Subjective outcomes
- (D) Blinding of outcome assessment (detection bias): Complications
- (E) Incomplete outcome data (attrition bias): Complications
- (F) Selective reporting (reporting bias)
- (G) Other bias

Length of hospital stay

Two studies including 104 participants measured length of hospital stay, but only one study including 44 participants had data suitable for reporting ([Hensle 1978](#)); the other study reported no difference between groups ([Daly 1982](#)).

We were uncertain if amino acid solution alone or in combination with dextrose solution had any effect on length of hospital stay (MD 0.5 days fewer; very low-quality evidence) ([Hensle 1978](#)). We downgraded the quality of evidence for study limitations, indirectness as the data used historic methods and very serious imprecision as the study was underpowered to demonstrate a clinically important difference of one day in length of hospital stay.

Secondary outcomes

Mortality

One study including 60 participants reported mortality ([Daly 1982](#)).

We were uncertain if amino acid solution alone or in combination with dextrose solution had any effect on mortality rates (RR approximately 1, CI not reported; very low-quality evidence). We downgraded the quality of evidence for study limitations, indirectness and there were too few events to reliably assess this outcome.

Comparison 6: branched chain amino acid solution and dextrose compared to dextrose only

We found one study including 19 participants that compared branched chain amino acids solution and dextrose to dextrose only (Bonau 1984). See [Summary of findings 6](#).

Primary outcomes

Complications up to 90 days after surgery

We were uncertain if branch chain amino acids solution and dextrose compared to dextrose had any effect on complication rates (RR approximately 1, CI not reported; very low-quality evidence). We downgraded the quality of evidence for study limitations, indirectness given that this study was conducted in the early 1980s and many important aspects of care related to patient population have changed, and for very serious imprecision. No complications reported in either group; therefore, no analysis was conducted.

Length of hospital stay

The study did not report length of hospital stay.

Secondary outcomes

Mortality

The study did not report mortality.

Comparison 7: perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement

We found one study including 61 participants that compared the provision of oral nutritional supplements three to four weeks preoperatively and four weeks postoperatively to multivitamin and mineral supplement (Ritch 2018). Follow-up was reported for a period of 30 days after surgery.

See [Summary of findings 7](#). All data for this comparison were obtained from the published report and the published protocol.

Primary outcomes

Complications up to 90 days after surgery

Perioperative oral supplements compared to an oral multivitamin and mineral supplement may have slightly decreased postoperative complications (RR 0.73, 95% CI 0.47 to 1.13; low-quality evidence; [Analysis 6.1](#)). We downgraded the quality of evidence for study limitations and imprecision. Assuming a baseline risk of postoperative complications of 66%, perioperative oral supplement would have resulted in 135 fewer occurrences per 1000 participants (95% CI 256 fewer to 65 more).

Length of hospital stay

Perioperative oral supplements compared to an oral multivitamin and mineral supplement may have had little or no effect on length of hospital stay (MD 0.30 days lower, 95% CI 3.64 lower to 3.04 more; low-quality evidence; [Analysis 6.2](#)). We downgraded quality of evidence for study limitations and the study was underpowered to demonstrate a clinically important difference of one day in length of hospital stay.

Secondary outcomes

Mortality

Perioperative oral supplements compared to an oral multivitamin and mineral supplement may have had little or no effect on postoperative mortality rates (RR 0.97, 95% CI 0.06 to 14.78; low-quality evidence; [Analysis 6.3](#)). We downgraded the quality of evidence for study limitations and imprecision. Assuming a baseline risk of postoperative mortality of 0.03, early feeding would have resulted in 1 fewer occurrences per 1000 participants (95% CI 31 fewer to 459 more).

Subgroup analysis

Subgroup analyses were not possible due to insufficient data.

Sensitivity analysis

Sensitivity analyses were not possible due to insufficient data.

DISCUSSION

Summary of main results

We identified eight RCTs which informed seven separate comparisons including 500 participants with bladder cancer undergoing an RC (Bonau 1984; Daly 1982; Deibert 2016; Hamilton-Reeves 2016; Hensle 1978; Ritch 2018; Roth 2013; Rovera 1989). The mean or median age of included participants was 61.5 to 69 (range 30 to 84) years. The majority of studies reported outcomes at 30 days (Hamilton-Reeves 2016; Ritch 2018; Roth 2013; Rovera 1989). One study reported outcomes up to 8 days postoperatively (Bonau 1984), one up to 60 days (Hensle 1978) and one to 90 days (Deibert 2016). In one study the follow up time was unclear (Daly 1982).

We found limited evidence that perioperative nutrition improved patient-important outcomes. Specifically, immuno-enhancing nutrition may have reduced 90-day complication rates (low-quality evidence). Preoperative oral nutrition support and amino acids with dextrose compared to dextrose alone may have reduced 30-day complication rates but we were uncertain of both these findings. PN when compared to oral nutrition may have increased complications (low-quality evidence) and so might postoperative feeding (very low-quality evidence), although we were very uncertain of the latter finding. Oral supplements given in the perioperative period may have slightly decreased postoperative complications (low-quality evidence); length of hospital stay may have been similar (low-quality evidence).

Overall completeness and applicability of evidence

This review excluded cohort studies and, therefore, the results do not reflect all the research in this area. There have been more-recent studies that have been single cohort reviews. We excluded studies that evaluated ERAS since the results of nutritional interventions could not be separated from the results of a multimodal approach to perioperative management.

The objective of this review was to assess the literature on the effects of perioperative nutrition in people undergoing RC for the treatment of bladder cancer on complications, length of hospital stay and mortality. Due to the lack of studies identified, this objective has only been partially met by the review. The included studies cover a period of almost 30 years during which time multiple changes have occurred in surgical technique and the

provision of artificial nutritional support. The included studies reflected the variety of approaches that have been devised to enhance the nutritional needs of people undergoing surgery.

One early study with a small sample size examined preoperative oral supplements but participants also had postoperative feeding with PN thus limiting the ability to assess the effect of the preoperative supplementation (Rovera 1989). There was no RCT evidence on enteral (nasogastric) feeding. One study examined PN and reported complications as an outcome in all participants postoperatively but showed this had an adverse effect on outcome measures (Roth 2013). We found no studies that evaluated PN in people with a non-functioning gut with or without malnutrition where PN would be potentially recommended in current clinical practice.

A more recent development in nutrition support is the use of specialised immuno-enhancing nutrition supplements and one study evaluated these supplements and found a reduction in complication and infection rates 90 days postsurgery but not at 30 days postsurgery; the study was a pilot study so had limited applicability without further replication (Hamilton-Reeves 2016). Although one study which evaluated early oral feeding in this group was unable to recruit the planned participants, it examined one of the nutrition elements of ERAS or 'fast track' protocols and showed that there was not an increase in complications after RC if early access to oral feeding was administered (Deibert 2016).

In summary, applicability of this review was severely limited by the paucity of studies, some of which were very old and therefore not directly applicable to today's patient population, RC practice and the type of nutritional interventions available. Interestingly, none of the studies looked at nutritional status as an inclusion criteria. Where nutritional interventions have been reported successful in other cancer settings (Burden 2017), participants had lost weight or were at particular risk or malnourished preoperatively.

Quality of the evidence

We consistently downgraded the quality of evidence for all six comparisons. The quality of evidence was rated as low to very low. Issues that lowered our confidence in the estimates of effect were study limitations, specifically unclear allocation concealment (selection bias) and the lack of blinding (performance and detection bias). We also frequently downgraded for imprecision due to small sample sizes and wide CIs. Some of the older studies made use of products which would no longer be used for nutrition support and we downgraded for indirectness. Due to the paucity of studies, we were unable to formally assess the possibility of publication bias.

Potential biases in the review process

Although we conducted this systematic review with a comprehensive search strategy identical with current standards of Cochrane, we found only eight RCTs. There is a possibility that despite our best efforts, we may have missed additional studies. This may be because they were published in languages other than English (although we applied no language restrictions), were published in non-indexed journals or were unpublished.

We contacted the study authors on several occasions and one provided feedback to our queries. However, we did not obtain data on standard deviations or standard errors that would have allowed

us to undertake more comprehensive analyses. This may represent a source of bias with potential under-reporting of the true effects of the interventions.

Three studies were listed as ongoing (see [Characteristics of ongoing studies](#) table); however, one was reported as having been completed (personal correspondence) and the other was due to have been completed. The reporting of results from these trials would have added to the information from this review.

Agreements and disagreements with other studies or reviews

We identified no systematic reviews specifically examining standard nutritional interventions in the perioperative treatment of people with bladder cancer undergoing an RC other than reviews of studies reporting nutritional intervention as part of ERAS protocols (Cerantola 2013; Maffezzini 2008; Melnyk 2011). We excluded studies reporting ERAS protocols from this review. Outcomes need to include both clinical outcomes and patient-reported outcomes with economic evaluations. We identified one review on immuno-enhancing nutrition, which concurred that there is a paucity in the literature regarding perioperative feeding in RC (Munbauhal 2014). This topic will have been partially answered by the reported small study on perioperative, preoperative and postoperative oral supplements (Hamilton-Reeves 2016). One review of people undergoing RC published since the initiation of this Cochrane Review identified preoperative nutrition optimisation and early postoperative feeding as important components that urologists should incorporate in a package of care for people undergoing this surgery (Matulewicz 2015).

AUTHORS' CONCLUSIONS

Implications for practice

Immuno-enhancing nutrition may reduce complication rates as may preoperative oral nutrition support and amino acids with dextrose (compared to dextrose alone) but we are uncertain of the latter two findings. Parenteral nutrition when compared to oral nutrition may increase complications (low-quality evidence) and so may postoperative feeding, although we are very uncertain of the latter finding. Length of hospital stay may not be impacted by any of the nutritional interventions for which we found randomised controlled trial (RCT) evidence.

Implications for research

This review highlights the need for better-quality research on the perioperative nutritional management of bladder cancer. Further research, particularly RCTs are required to evaluate nutritional interventions pre- and postoperatively in the surgical treatment of people diagnosed with muscle-invasive bladder cancer requiring radical cystectomy. There is a paucity of research evaluating oral and enteral nutritional support in this group using robust research methods. Parenteral nutrition needs to be evaluated further in people who are malnourished following surgery where the feeding regimens are calculated to meet individual requirements. It is also important to consider the risks of refeeding syndrome (a metabolic response to overfeeding after a period of nutritional deprivation).

Specific comparisons which require further research include:

- preoperative nutritional support using oral supplements compared to standard diet;
- postoperative oral nutritional support compared to standard diet;
- immuno-enhancing nutrition supplements compared to standard nutrition supplements;
- parenteral nutrition requires further evaluation in the postoperative period where participants have a non-functioning gastrointestinal tract in early compared to late provision of feeding;
- patient-reported outcomes and quality of life measures need to be incorporated into future research as outcome measures;
- body composition measurements along with measures of nutritional status need to be included in trials to determine if the interventions are altering nutritional status and body composition.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Bonau 1984

Methods	<p><u>Study design</u>: parallel-group randomised controlled trial</p> <p><u>Study dates</u>: not reported</p> <p><u>Setting</u>: Memorial Sloan-Kettering Centre, New York, NY, USA</p>
Participants	<p><u>Inclusion criteria</u>: men with stage I bladder cancer who underwent a radical cystectomy and an ileal conduit diversion.</p>

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy (Review)

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Bonau 1984 (Continued)

Exclusion criteria: men with metastatic disease, cirrhosis, hepatitis, diabetes or renal failure

Total number of participants randomly assigned: 19

Age: range 46–76 years

Sex: men

Nutrition status: participants were judged to be of normal nutrition status with no prior weight loss (no further details reported)

Group 1: intravenous dextrose

Number of all participants randomly assigned: 4

Age: not reported

Sex: men

Tumour stage/grade: not reported

Comorbidities: not reported

Group 2: intravenous dextrose and a commercially available amino acid solution containing 25% branched chain amino acids

Number of all participants randomly assigned: 9

Age: not reported

Sex: men

Tumour stage/grade: not reported

Comorbidities: not reported

Group 3: intravenous dextrose and a commercially available amino acid solution enriched with 45% branched chain amino acids

Number of all participants randomly assigned: 6

Age: not reported

Sex: men

Tumour stage/grade: not reported

Comorbidities: not reported

Group 4: see 'Notes' below

Interventions

All groups: intravenous solutions as detailed below, but containing similar amounts of electrolytes, trace minerals and vitamins. Infusions began at 8 a.m. postoperative day 1 and infusions were stopped at postoperative day 8. During the 7-day postoperative study period, none of the participants had any oral intake

Group 1 (n = 4): 150 g dextrose in 3 L of water administered intravenously over 24 hours.

Group 2 (n = 9): intravenous dextrose solution and a commercially available amino acid solution containing 25% branched chain amino acids (Aminosyn 7%; Abbott Laboratories). Administration rates were designed to deliver 30 kcal/kg/day and 1.5g protein/kg/day.

Group 3 (n = 6): intravenous dextrose solution and an amino acid solution enhanced with 45% branched chain amino acids. Administration rates were designed to deliver 30 kcal/kg/day and 1.5g protein/kg/day.

Bonau 1984 (Continued)

Outcomes	<u>Complications</u> : no participants had sepsis or wound infection during the postoperative study period. Postoperative ileus is reported to have occurred but there is no reporting on the number of participants affected. How measured: not reported Time point measured: not reported Time point reported: at the end of the postoperative study period (day 8) <u>Length of hospital stay</u> : not reported <u>Mortality</u> : not reported	
Funding sources	Supported in part by a National Institute Health grant and by a grant from Abbott Laboratories	
Declarations of interest	No declarations of interest reported	
Notes	<u>Language of publication</u> : English A 4th group comprising of 6 participants was studied but not included above as this group consisted of consecutive referrals and not randomly assigned participants.	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported to have occurred but not fully described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality not reported.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding reported.
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Length of hospital stay	Unclear risk	Length of hospital stay not reported.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Mortality not reported.
Incomplete outcome data (attrition bias) Complications	Unclear risk	Reporting unclear and data not available by group.

Bonau 1984 (Continued)

Incomplete outcome data (attrition bias) Length of hospital stay	Unclear risk	Length of hospital stay not reported.
Incomplete outcome data (attrition bias) Mortality	Low risk	Mortality not reported.
Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No other bias detected.

Daly 1982

Methods	<u>Study design</u> : parallel-group randomised controlled trial <u>Study dates</u> : not reported <u>Setting</u> : Memorial Sloan-Kettering Centre, New York, NY, USA
Participants	<u>Inclusion criteria</u> : undergoing a radical cystectomy and ileal loop diversion following preoperative radiotherapy for bladder cancer <u>Exclusion criteria</u> : not reported <u>Total number of participants randomly assigned</u> : 93 <u>Age</u> : mean age across groups 61–63 years <u>Sex</u> : not reported, but described as similar in each group <u>Nutrition status</u> : mean % ideal bodyweight was 107–108 although it was unclear if this was at baseline. Group 1: intravenous dextrose <u>Number of all participants randomly assigned</u> : 30 <u>Age</u> : not reported <u>Sex</u> : not reported <u>Tumour stage/grade</u> : not reported <u>Comorbidities</u> : not reported Group 2: intravenous fluids containing amino acids <u>Number of all participants randomly assigned</u> : 30 <u>Age</u> : not reported <u>Sex</u> : not reported <u>Tumour stage/grade</u> : not reported <u>Comorbidities</u> : not reported Group 3: intravenous dextrose and amino acids solution <u>Number of all participants randomly assigned</u> : 30

Daly 1982 (Continued)

	<u>Age</u> : not reported <u>Sex</u> : not reported <u>Tumour stage/grade</u> : not reported <u>Comorbidities</u> : not reported
Interventions	<u>All groups</u> : interventions were given from 3 days preoperatively until a minimum of 7 days postoperatively <u>Group 1</u> (n = 30): intravenous dextrose solution <u>Group 2</u> (n = 30): intravenous fluids containing 1.3–1.5 g/kg/day amino acids <u>Group 3</u> (n = 30): intravenous dextrose plus 1.3–1.5 g/kg/day amino acids
Outcomes	<u>Complications</u> : unspecified complications were reported in 17% (group 1), 18% (group 2) and 17% (group 3) How measured: not reported Time point measured: not reported Time point reported: at the end of the study period <u>Length of hospital stay</u> : reported as similar in all groups How measured: not reported Time point measured: not reported Time point reported: not reported <u>Mortality</u> : no deaths during the study period How measured: number of deaths Time point measured: not reported Time point reported: at end of the study period
Funding sources	Not reported
Declarations of interest	No declarations of interest reported
Notes	<u>Language of publication</u> : English 93 participants cited as the total number randomised to 3 groups with 30 in each group. There were 3 participants unaccounted for in the report. The study was briefly described as the report was a short abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Process of allocation not described.

Daly 1982 (Continued)

Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality not likely to be affected by blinding.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	No blinding described.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assessment of mortality unlikely to be affected by blinding.
Incomplete outcome data (attrition bias) Complications	Low risk	93 participants randomised and 90 participants reported in analysis.
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	93 participants randomised and 90 participants reported in analysis.
Incomplete outcome data (attrition bias) Mortality	Low risk	93 participants randomised and 90 participants reported in analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol seen.
Other bias	Low risk	No other bias detected.

Deibert 2016

Methods	<u>Study design:</u> randomised controlled trial <u>Study dates:</u> 2011–2014 <u>Setting:</u> 2 large hospitals in USA
Participants	<u>Inclusion criteria:</u> adults undergoing radical cystectomy and urinary diversion for bladder cancer <u>Exclusion criteria:</u> not reported <u>Total number of participants randomly assigned:</u> 102 <u>Age:</u> not reported <u>Sex:</u> 84 men, 18 women <u>Nutrition status:</u> not reported

Deibert 2016 (Continued)

Group 1: early feeding group

Number of participants randomly assigned: 50

Age: not reported

Sex: 37 men, 13 women

Tumour stage/grade:

T0: n = 0; Ta: n = 3; T1: n = 15; T2: n = 22; T3: n = 1; T4: n = 1

Node positive: n = 3

Comorbidities: diabetes: n = 6

Group 2: standard postoperative care

Number of participants randomly assigned: 52

Age: not reported

Sex: 47 men, 5 women

Tumour stage/grade:

T0: n = 1; Ta: n = 0; T1: n = 12; T2: n = 23; T3: n = 6; T4: n = 0

Node positive: n = 1

Comorbidities: diabetes: n = 12

Interventions

All groups: both groups had prokinetic medications, early ambulation and no nasogastric tube. Participants with nausea were advised to decrease their intake of the allocated diet. Where vomiting occurred on oral intake, oral intake was withheld for 8 hours and then clear liquid diet was resumed. Where nasogastric tube decompression was needed for persistent vomiting, standard diet was instigated after tube removal.

Group 1 (n = 50): early feeding group given clear liquid diet on postoperative day 1 and access to full normal diet on postoperative day 2

Duration: from postoperative day 1 onwards

Group 2 (n = 52): standard postoperative care not part of a specific fast track pathway including nil by mouth status until either flatus or bowel sounds

Duration: postoperatively onwards

Outcomes
Postoperative complications

How measured: using Clavien system

Time point measured: not reported

Time point reported: not reported

Rates of ileus: how many participants had ileus

How measured: defined as ≥ 3 days from the induction of food until tolerance or if nasogastric tube insertion was required due to persistent vomiting prior to or after any introduction of food.

Time point measured: up to 90 days postoperatively

Time point reported: up to 90 days postoperatively

Length of hospital stay: reported as not significantly different between groups

Deibert 2016 (Continued)

How measured: number of days

Time point measured: number of days in hospital

Time point reported: not reported

Mortality: 2 deaths in group 1 and 4 deaths in group 2

How measured: number of deaths

Time point measured: up to 90 days postoperatively

Time point reported: up to 90 days postoperatively

Funding sources	Not described
Declarations of interest	No declarations of interest reported.
Notes	<u>Language of publication</u> : English This study was terminated before reaching the planned recruitment numbers due to slow accrual of participants.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The process of random sequence generation was not described in the published study but a process of random sequence generation was described in the protocol.
Allocation concealment (selection bias)	Unclear risk	Method of allocation not described.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality unlikely to be affected by blinding.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	No blinding described.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Mortality unlikely to be affected by lack of blinding.
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised participants were included in the analysis of complications.

Deibert 2016 (Continued)

Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	All randomised participants were included in the analysis of length of hospital stay.
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised participants were included in the analysis of mortality.
Selective reporting (reporting bias)	Low risk	The outcomes planned in the protocol were reported although fewer statistical tests than planned in the protocol could be done due to the trial being terminated prior to recruitment of planned numbers of participants.
Other bias	Low risk	No other bias detected.

Hamilton-Reeves 2016

Methods	<u>Study design</u> : randomised controlled trial <u>Study dates</u> : September 2013 to April 2015 <u>Setting</u> : hospital, Kansas City, MO, USA
Participants	<u>Inclusion criteria</u> : people undergoing radical cystectomy for primary bladder cancer <u>Exclusion criteria</u> : swallowing difficulties, metastasis, $\geq 10\%$ weight loss in previous 6 months, BMI < 18.5 , viral infection, immune deficiency, gout or relevant food allergies <u>Total number of participants randomly assigned</u> : 29 <u>Age</u> : not reported <u>Sex</u> : men <u>Comorbidities</u> : assessed using the Charlson Comorbidity Index <u>Nutrition status</u> : assessed using the PG-SGA validated tool and BMI calculated. Group 1: immunonutrition <u>Number of participants randomly assigned</u> : 14 <u>Age</u> : mean age 69.6 (SD 7.1) years <u>Sex</u> : men <u>Tumour stage/grade</u> : Ta: n = 1; Tis: n = 0; T1: n = 2; T2: n = 11 <u>Comorbidities</u> : mean index result 4.9 <u>Nutrition status</u> : mean BMI 26, mean PG-SGA score 6.7 Group 2: oral nutritional supplements <u>Number of participants randomly assigned</u> : 15 <u>Age</u> : mean age (SD) 68.1 (8.0) years <u>Sex</u> : men <u>Tumour stage/grade</u> : Ta: n = 2; Tis: n = 2; T1: n = 2; T2: n = 7 <u>Comorbidities</u> : mean index result was 5.1

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy (Review)

Hamilton-Reeves 2016 (Continued)

Nutrition status: mean BMI 29, mean PG-SGA score 5.5

Interventions	<p><u>All groups</u>: nutrition supplements given for 5 days preoperatively and 5 days postoperatively at dose 3 cartons per day</p> <p><u>Group 1</u>: immunonutrition supplement drinks</p> <p><u>Group 2</u>: oral nutrition supplement drinks</p>
Outcomes	<p><u>Postoperative complications</u></p> <p>Measured: graded according to Clavien-Dindo scheme (Dindo 2004)</p> <p>Time point measured: ≤ 30 days and 31–90 days after surgery</p> <p>Time point reported: 30 and 90 days after surgery</p> <p><u>Infection rates</u></p> <p>Measured: defined by the need for intervention or prescription</p> <p>Time point measured: ≥ 30 and 31–90 days after surgery</p> <p>Time point reported: 30 and 90 days after surgery</p> <p><u>Length of hospital stay</u></p> <p>Measured: number of days</p> <p>Time point measured: up to discharge</p> <p>Time point reported: up to discharge</p> <p><u>Mortality</u>:</p> <p>Measured: number of deaths</p> <p>Time point: measured up to 90 days postoperatively</p> <p>Time point reported: up to 90 days postoperatively</p>
Funding sources	<p>American Cancer Society</p> <p>Nestle Healthcare Research grant</p> <p>KL2 Scholars Award</p> <p>Nestle HealthCare Nutrition provided the supplement drinks</p>
Declarations of interest	Research funding from Nestle Healthcare and travel support received by Hamilton-Reeves.
Notes	<p><u>Language of publication</u>: English</p> <p>Some data for this study were published in supplementary tables to the published paper.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation was done "using a computer generated randomisation list administered by a statistician who was not involved in the implementation of the study." Adequate sequence generation.

Hamilton-Reeves 2016 (Continued)

Allocation concealment (selection bias)	Low risk	Allocation list was "only accessible to study coordinator via password-protected computer database."
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality rates unlikely to be affected by blinding.
Blinding of participants and personnel (performance bias) Subjective outcomes	Low risk	Supplement cartons were wrapped with opaque tape and numbered by staff not involved in patient care or data collection so the intervention was masked.
Blinding of outcome assessment (detection bias) Complications	Low risk	Supplement cartons were wrapped with opaque tape and numbered by staff not involved in patient care or data collection so the intervention was masked.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Assessment of length of hospital stay unlikely to be affected by blinding.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assessment of mortality rates unlikely to be affected by blinding.
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised participants included in analysis of complications.
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	All randomised participants included in analysis of length of hospital stay.
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised participants included in analysis of mortality.
Selective reporting (reporting bias)	Low risk	In the protocol recorded on www.clinicaltrials.gov , all planned outcomes were reported.
Other bias	Low risk	No other bias detected.

Hensle 1978

Methods	<u>Study design:</u> parallel-group randomised controlled trial <u>Study dates:</u> not reported <u>Setting:</u> Columbia-Presbyterian Medical Centre, New York, NY, USA
Participants	<u>Inclusion criteria:</u> people undergoing radical cystectomy and urinary diversion for invasive bladder cancer <u>Exclusion criteria:</u> people with renal failure or insulin-dependent diabetes, or both <u>Total number of participants randomly assigned:</u> 44

Hensle 1978 (Continued)

Age: not reported

Sex: not reported

Nutrition status: 17 participants were defined by the study authors as having 'nutritional depletion' prior to operation.

Group 1: fluid management with 5% dextrose solution

Number of all participants randomly assigned: 15

Age: not reported

Sex: not reported

Tumour stage/grade: not reported

Comorbidities: not reported

Nutrition status: 6 participants were nutritionally depleted preoperatively.

Group 2: crystalline amino acid solution

Number of all participants randomly assigned: 29

Age: not reported

Sex: not reported

Tumour stage/grade: not reported

Comorbidities: not reported

Nutrition status: 11 participants were nutritionally depleted.

Interventions

Both groups: vitamins and minerals were given with both preparations.

Duration of intervention not described

Group 1 (n = 15): postoperative fluid management of 5% dextrose solution along with balanced electrolytes and whole blood and blood byproducts as necessary. Participants began oral intake as clinical status indicated.

Group 2 (n = 29): crystalline amino acid solution containing a 3% mixture of essential and non-essential amino acids with appropriate micronutrient and cofactors designed to deliver 0.7–1.0 g/kg/24 hours of amino acid with a calorie value of approximately 240 kcal/day; also electrolytes and whole blood and blood byproducts as necessary. This supplementation continued until the participants were able to meet their energy needs orally.

Outcomes

Postoperative complications: occurred in 33% of participants in group 1 and in 17% of participants in group 2

How measured: not reported but included sepsis, wound dehiscence and renal failure

Time point measured: not reported

Time point reported: not reported

Length of hospital stay: group 1: mean 32 days, range 17–66 days; group 2: mean 27 days, range 16–44 days

How measured: number of days in hospital

Time point measured: not reported

Time point reported: not reported

Hensle 1978 (Continued)

Mortality: no deaths in either group.

How measured: number of deaths

Time point measured: up to 60 days after surgery

Time point reported: not reported

Funding sources	Supported by a grant from the Medical Department, McGaw Laboratories.
Declarations of interest	No declarations of interest reported
Notes	<u>Language of publication</u> : English 30 participants received preoperative radiotherapy. 4 participants in Group 1 had to be switched to total PN.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Primary physicians changed some group allocations.
Allocation concealment (selection bias)	High risk	Primary physicians changed some group allocations.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding unlikely to affect outcome.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	No blinding described.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assessment of mortality unlikely to be affected by blinding.
Incomplete outcome data (attrition bias) Complications	Low risk	All participants randomised were reported in the analysis.
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	All participants randomised were reported in the analysis
Incomplete outcome data (attrition bias)	Low risk	All participants randomised were included in the analysis.

Hensle 1978 (Continued)

Mortality

Selective reporting (reporting bias)	Unclear risk	No protocol available.
Other bias	Low risk	No further bias detected.

Ritch 2018

Methods	<u>Study design</u> : parallel-group randomised controlled trial <u>Study dates</u> : April 2014 to December 2016 <u>Setting</u> : Vanderbilt University Medical Center, Nashville, TN, USA
Participants	<u>Inclusion criteria</u> : people with urothelial carcinoma of the bladder <u>Exclusion criteria</u> : people who were not surgical candidates <u>Total number of participants randomly assigned</u> : 61 <u>Age</u> : ≥ 18 years <u>Sex</u> : 54 men, 7 women <u>Performance status</u> : Eastern Cooperative Oncology Group performance status ≤ 3 Group 1: oral nutritional supplements <u>Number of all participants randomly assigned</u> : 31 <u>Age</u> : mean 69 (SD 14.1) years <u>Sex</u> : 26 men, 5 women <u>Tumour stage</u> : $\leq T1$: n = 14; T2: n = 11; T3–T4: n = 6 <u>Comorbidities</u> : Charlson Comorbidity Index: 0: n = 13; 1: n = 7; 2: n = 8; ≥ 3 : n = 3 <u>Nutrition status</u> : mean BMI 27.8 (SD 17.9) Group 2: multivitamin and minerals <u>Number of all participants randomly assigned</u> : 30 <u>Age</u> : mean 66.7 (SD 9.6) years <u>Sex</u> : 28 men, 2 women <u>Tumour stage/grade</u> : $\leq T1$: n = 17; T2: n = 9; T3–T4: n = 4 <u>Comorbidities</u> : Charlson Comorbidity Index: 0: n = 14; 1: n = 8; 2: n = 4, ≥ 3 : n = 4 <u>Nutrition status</u> : mean BMI 29.3 (SD 5.5)
Interventions	<u>Both groups</u> : intervention was given for 3–4 weeks preoperatively and 4 weeks postoperatively <u>Group 1</u> (n = 31): oral nutritional supplement group received Ensure Clinical Strength, Abbott Nutrition 1 serving twice daily

Ritch 2018 (Continued)

Group 2 (n = 30): multivitamin and mineral group received 1 serving twice daily

Outcomes	<p><u>Complications</u></p> <p>How measured: Clavien-Dindo classification system (Dindo 2004)</p> <p>Time point measured: up to 30 days</p> <p>Time point reported: up to 30 days</p> <p><u>Length of hospital stay</u>: reported in days</p> <p><u>Mortality</u>:</p> <p>How measured: confirmation of obituary statement</p> <p>Time point measured: 30 days</p> <p>Time point reported: 30 days</p>
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Funding sources	Supported by Vanderbilt CTSA, NIH National Centre and Abbott Nutrition Award
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Declarations of interest	None reported
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Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding unlikely to affect outcome.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding reported.
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding reported.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Assessment of length of hospital stay unlikely to be influenced by blinding.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assessment of mortality unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias)	Low risk	8 participants were not included in reporting complications; 1 participant died and surgery was aborted, and 7 participants withdrew

Ritch 2018 (Continued)

Complications

Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	8 participants were not included in reporting length of hospital stay; 1 participant died and surgery was aborted, and 7 participants withdrew
Incomplete outcome data (attrition bias) Mortality	Low risk	8 participants were not included in reporting mortality; 1 participant died and surgery was aborted, and 7 participants withdrew
Selective reporting (reporting bias)	Low risk	In the protocol recorded on www.clinicaltrials.gov , all planned outcomes were reported.
Other bias	Low risk	

Roth 2013

Methods	<u>Study design</u> : parallel-group randomised controlled trial <u>Study dates</u> : September 2008 to March 2011 <u>Setting</u> : University Hospital Bern, Bern, Switzerland
Participants	<u>Inclusion criteria</u> : people undergoing radical cystectomy and ileal diversion <u>Exclusion criteria</u> : previous lymph node dissection, chronic inflammatory bowel disease, radiotherapy, prior bowel surgery, severe hepatic or cardiac dysfunction, inability to consent <u>Total number of participants randomly assigned</u> : 157 <u>Sex</u> : 106 men, 51 women <u>Age</u> : group 1: median 67 (range 34–80) years; group 2: median 66 (range 30–86) years <u>Tumour stage/grade</u> : not reported <u>Comorbidities</u> : 14 participants had diabetes, 51 participants had an ASA score III/IV <u>Nutrition status</u> : 34 participants were defined as malnourished based on defined criteria. Group 1: PN <u>Number of all participants randomly assigned</u> : 74 <u>Age</u> : median 67 (range 34–80) years <u>Sex</u> : 53 men, 21 women <u>Tumour stage/grade</u> : not reported <u>Comorbidities</u> : diabetes 8%, ASA score III/IV 31% <u>Nutrition status</u> : malnourished 15% Group 2: oral nutrition alone <u>Number of all participants randomly assigned</u> : 83 <u>Age</u> : median 66 (range 30–86) years <u>Sex</u> : 53 men, 30 women

Roth 2013 (Continued)

	<p><u>Tumour stage/grade</u>: not reported</p> <p><u>Comorbidities</u>: diabetes 10%, ASA score III/IV 34%</p> <p><u>Nutrition status</u>: malnourished 28%</p>
Interventions	<p><u>Both groups</u>: 5% glucose solution administered intravenously for the first 5 postoperative days. Oral intake was introduced on postoperative day 1 in both groups with a gastrostomy tube in place, initially left on drainage. Solid diet was resumed when bowel sounds returned and when fluids were tolerated.</p> <p><u>Group 1</u> (n = 74): PN (Nutriflex special 70/240, B Braun Medical, Melsungen, Germany). All participants received 1500 mL/day for 5 days postoperatively (containing 1860 kcal, 105 g polyamino acids, 360 g glucose and 0 g lipid)</p> <p><u>Group 2</u> (n = 83): oral nutrition with Ringer's lactate solution (Sintetica-Bioren, Switzerland); 1500 mL/24 hours and additional potassium substitute (40 mmol)</p>
Outcomes	<p><u>Complications</u></p> <p>How measured: according to the Clavien-Dindo classification (Dindo 2004)</p> <p>Time point measured: up to 30 days after surgery</p> <p>Time point reported: up to 30 days</p> <p><u>Length of hospital stay</u>: reported as not differing between the 2 groups</p> <p>How measured: number of days in hospital</p> <p>Time point measured: at discharge from hospital</p> <p>Time point reported: number of days prior to discharge</p> <p><u>Mortality</u>: 1 participant in each group died from complications</p> <p>How measured: number of deaths</p> <p>Time point measured: up to 30 days postoperatively</p> <p>Time point reported: up to 30 days postoperatively</p>
Funding sources	None
Declarations of interest	None declared
Notes	<p><u>Language of publication</u>: English</p> <p>Study was terminated early before enrolment targets were met following an interim statistical analysis.</p>
Risk of bias	
Bias	Authors' judgement Support for judgement
Random sequence generation (selection bias)	<p>Low risk</p> <p>Quote: "Randomly allocated by a computer-based program."</p> <p>Comment: adequate sequence generation.</p>
Allocation concealment (selection bias)	<p>Unclear risk</p> <p>Not described.</p>
Blinding of participants and personnel (performance bias)	<p>Low risk</p> <p>Mortality rates unaffected by blinding.</p>

Roth 2013 (Continued)

Objective outcomes

Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding reported.
Blinding of outcome assessment (detection bias) Complications	Low risk	Assessed by a blinded study nurse.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Assessment of length of hospital stay unlikely to be influenced by blinding.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assessment of mortality unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised participants were included in the assessment of complications.
Incomplete outcome data (attrition bias) Length of hospital stay	Low risk	All randomised participants were included in the assessment of length of hospital stay.
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised participants were included in the assessment of mortality.
Selective reporting (reporting bias)	Unclear risk	No protocol seen, outcomes described in the methods section of the publication were reported.
Other bias	Low risk	No other bias detected.

Rovera 1989

Methods	<u>Study design:</u> parallel-group randomised controlled trial <u>Study dates:</u> not reported <u>Setting:</u> Turin, Italy
Participants	<u>Inclusion criteria:</u> people undergoing radical cystectomy for bladder cancer <u>Exclusion criteria:</u> not reported <u>Number of all participants randomly assigned:</u> 28 <u>Age:</u> not reported <u>Sex:</u> 22 men, 6 women <u>Tumour stage/grade:</u> not reported <u>Comorbidities:</u> not reported <u>Nutrition status:</u> not reported

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy (Review)

Rovera 1989 (Continued)

Group 1: preoperative nutrition supplementation

Number of all participants randomly assigned: 12

Age: median 66.1 (range 45–78) years

Sex: 9 men, 3 women

Tumour stage/grade: not reported

Comorbidities: not reported

Group 2: normal hospital diet preoperatively

Number of all participants randomly assigned: 16

Age: median 65.1 (range 47–80) years

Sex: 13 men, 3 women

Tumour stage/grade: not reported

Comorbidities: not reported

Nutrition status: not reported

Interventions	<p><u>Both groups:</u> postoperative PN commenced 1 day after surgery and continued for 14 days administered via a central line. PN calculated to provide 49 kcal/kg/day and 1.7 g protein/kg/day with a nitrogen:total calorie ratio 1:170 and with energy provided as 80% glucose and 20% fat plus vitamins, minerals and trace elements.</p> <p><u>Group 1</u> (n = 12): preoperative oral nutritional support for 10 days prior to surgery comprised of an interview with a dietitian about usual diet and the provision of a personalised diet based on normal food combined with a supplement including a multivitamin and mineral preparation (Precision N). The supplement provided 30 kcal/kg/day and 1.5 g protein/kg/day.</p> <p><u>Group 2</u> (n = 16): normal hospital diet up to day of operation.</p>
Outcomes	<p><u>Complications</u></p> <p>How measured: not reported</p> <p>Time point measured: up to 30 days postsurgery</p> <p>Time point reported: up to 30 days postsurgery</p> <p><u>Length of hospital stay:</u> not reported</p> <p><u>Mortality:</u> no deaths reported</p> <p>How measured: number of deaths</p> <p>Time point measured: up to 30 days postsurgery</p> <p>Time point reported: up to 30 days postsurgery</p>
Funding sources	Not reported
Declarations of interest	Not reported
Notes	<p><u>Language of publication:</u> Italian</p> <p>No information on dietary intake in the report. Some parts of the report were not translated in sufficient detail to extract all the details.</p>

Rovera 1989 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described.
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding unlikely to affect outcome.
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding described and these outcomes could have been influenced as reporting involves judgement.
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding described.
Blinding of outcome assessment (detection bias) Length of hospital stay	Low risk	Length of hospital stay not reported.
Blinding of outcome assessment (detection bias) Mortality	Low risk	Assessment of mortality unlikely to be influenced by blinding.
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised participants were included in the assessment of complications.
Incomplete outcome data (attrition bias) Length of hospital stay	Unclear risk	Length of hospital stay not reported.
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised participants were included in the assessment of mortality.
Selective reporting (reporting bias)	Unclear risk	No protocol seen. Outcomes described in the methods were reported.
Other bias	Low risk	No other bias detected.

ASA: American Society of Anesthesiologists; BMI: body mass index; n: number of participants; PG-SGA: Patient-Generated Subjective Global Assessment; PN: parenteral nutrition; SD: standard deviation.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Brodner 2001	No comparison of a nutritional intervention during the randomised phase of this trial, which investigated the perioperative management of people undergoing radical cystectomy. Therefore, this study did not meet the inclusion criteria.
Daly 1987	Partially randomised trial examining postoperative jejunostomy feeding. The measured outcomes compared groups where randomisation did not occur. Therefore, this trial did not meet the inclusion criteria.
de Vries 2012	Not an RCT therefore excluded.
Hensle 1985	RCT reporting only biochemical outcomes. Therefore did not report the outcomes specified for this review.
Karl 2014	In this RCT nutrition supplements and the early introduction of foods postoperatively were used as part of an ERAS Intervention. The study was excluded as it would not have been possible to separate out the effects of the nutrition intervention from the other interventions.
Malossini 1987	Not an RCT, therefore did not meet our inclusion criteria. It was a comparison of differing types of parenteral nutrition given to 2 non-randomised groups of participants postcystectomy
Mangano 1993	Not an RCT, therefore did not meet our inclusion criteria. 2 groups of participants who had undergone radical cystectomy were given total parenteral nutrition with or without glutamine supplementation.
McArdle 1986	Not an RCT, therefore did not meet our inclusion criteria. Although this study was commenced as an RCT, after enrolment of the fourth participant, the protocol was modified to result in a cohort study with retrospective controls. The study investigated the use of elemental diet in people undergoing radiotherapy and associated radical cystectomy.
Olbert 2009	Did not meet our inclusion criteria as there was no comparison of a nutritional intervention in this RCT, which compared alternate modes of perioperative management of people undergoing radical cystectomy.
Solomon 1978	Did not meet our inclusion criteria. In this RCT examining 3 hypocaloric regimens in people undergoing urological surgery, 47% had radical cystectomy for bladder cancer.

ERAS: Enhanced Recovery After Surgery; RCT: randomised controlled trial.

Characteristics of ongoing studies *[ordered by study ID]*

NCT02238886

Trial name or title	Radical cystectomy, nutrition and convalescence: can goal-directed postoperative nutritional therapy reduce the convalescence period for patients undergoing radical cystectomy (RC)?
Methods	Randomised controlled trial with parallel assignment
Participants	Adults aged > 18 years undergoing radical cystectomy who are able to give informed consent (excluded if previous radiotherapy at the pelvic area, ureterocutaneostomy or robot-assisted surgery.
Interventions	<p>Group 1: goal-directed nutritional intervention combining oral intake and parenteral nutrition using a parenteral nutritional intervention: dietary supplement is parenteral nutrition in central vein (SMOFKABIVEN; Fresenius Kabi)</p> <p>Group 2: standard nutritional treatment of resting the bowel until there are signs of bowel recovery and then feeding orally</p>

NCT02238886 (Continued)

Outcomes	<p>Primary outcome: quality of life using validated questionnaires.</p> <p>Secondary outcomes: bodyweight, hand grip strength, biochemical measures, length of hospital stay and time to bowel recovery.</p> <p>Follow-up: 12 weeks</p>
Starting date	May 2012
Contact information	Line Noes Lydom, Rigshospitalet, Denmark
Notes	Above details extracted from www.clinicaltrials.gov . Data collection completed in December 2013, 36 participants have been recruited. Data awaiting preparation for publication (email from contact author July 2017, no further updates received July 2018).

NCT03147586

Trial name or title	Influence of immune nutrition diet on 90-day outcomes in patients undergoing radical cystectomy
Methods	Randomised double-blind placebo-controlled phase IV trial with 2 parallel treatment groups
Participants	Adults aged ≥ 18 years diagnosed with bladder cancer eligible for radical cystectomy and urinary diversions. Estimated enrolment 100 participants.
Interventions	<p>Group 1: Bio-tech and omega-3 plus Bio-tech (Biopharm pharmaceutical) powder 30 mg 3 times daily (contains multivitamins and essential amino acids) plus omega-3 plus (SEDICO pharmaceutical) capsules 3 times daily (source for omega-3 fatty acids) 1 week before and 2 weeks after surgery</p> <p>Group 2: placebo powder 30 mg 3 times daily plus placebo capsules 3 times daily for 1 week before and 2 weeks after surgery</p>
Outcomes	<p>Primary outcome: overall 90-day postoperative complication between groups measured by modified Dindo-Clavien system (Dindo 2004)</p> <p>Secondary outcomes: validated nutritional assessment scores at 90 days and anthropometric measures measured by skinfold thickness at 90 days</p>
Starting date	March 2017
Contact information	<p>Abdelwahab R Hashem, MSc</p> <p>Mansoura, Aldakahlia, Egypt, 35516</p>
Notes	Above details extracted from www.clinicaltrials.gov . Data collection completed in October 2017.

NCT03204266

Trial name or title	Oral supplementation to enhance recovery pilot study
Methods	Randomised parallel assignment interventional clinical trial
Participants	Radical cystectomy for bladder cancer with urinary diversion, aged ≥ 18 years, 46 participants
Interventions	Group 1: immunonutrition: arginine + omega-3 fatty acids. Participants take 30 mL of arginine recovery supplement 4 times daily 5 days preoperatively and 14 days postoperatively.

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy (Review)

NCT03204266 (Continued)

Participants also given omega-3 fatty acids, 1 g 4 times daily, 4 g total daily. This will be started 7 days preoperatively and continued 14 days postoperatively.

Group 2: no immunonutrition

Outcomes	<p>Primary outcome: participant compliance at 21 days after starting immunonutrition regimen. Defined as 'Yes' if a participant completes ≥ 16 out of the total 21 days' treatment.</p> <p>Secondary outcomes: length of hospital stay > 7 days, postoperative infections, hospital readmissions, deaths within 90 days of cystectomy all at 90 days after surgery; decrease in inflammatory response of serum interleukin-6 levels after radical cystectomy postoperative day 1</p>
Starting date	17 January 2018
Contact information	Neema Navai, MD Anderson Cancer Center National Cancer Institute (NCI)
Notes	Estimated completion August 2019

DATA AND ANALYSES

Comparison 1. Postoperative parenteral nutrition compared to standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications	1	157	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.07, 1.82]
2 Mortality	1	157	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.07, 17.62]

Analysis 1.1. Comparison 1 Postoperative parenteral nutrition compared to standard care, Outcome 1 Complications.

Study or subgroup	Parenteral nutrition n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Roth 2013	51/74	41/83		100%	1.4[1.07,1.82]
Total (95% CI)	74	83		100%	1.4[1.07,1.82]
Total events: 51 (Parenteral nutrition), 41 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.45(P=0.01)					

Analysis 1.2. Comparison 1 Postoperative parenteral nutrition compared to standard care, Outcome 2 Mortality.

Comparison 2. Immunonutrition compared to standard oral nutritional supplements

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications at 90 days	1	29	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.08, 1.23]
2 Complications at 30 days	1	29	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.62, 1.53]
3 Length of hospital stay	1	29	Mean Difference (IV, Random, 95% CI)	0.20 [-1.69, 2.09]

Analysis 2.1. Comparison 2 Immunonutrition compared to standard oral nutritional supplements, Outcome 1 Complications at 90 days.

Analysis 2.2. Comparison 2 Immunonutrition compared to standard oral nutritional supplements, Outcome 2 Complications at 30 days.

Analysis 2.3. Comparison 2 Immunonutrition compared to standard oral nutritional supplements, Outcome 3 Length of hospital stay.

Comparison 3. Preoperative oral nutritional support compared to normal diet

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications	1	28	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.18, 4.51]

Analysis 3.1. Comparison 3 Preoperative oral nutritional support compared to normal diet, Outcome 1 Complications.

Comparison 4. Early postoperative feeding compared to standard postoperative management

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications	1	102	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.85, 1.53]
2 Mortality	1	102	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.10, 2.71]

Analysis 4.1. Comparison 4 Early postoperative feeding compared to standard postoperative management, Outcome 1 Complications.

Analysis 4.2. Comparison 4 Early postoperative feeding compared to standard postoperative management, Outcome 2 Mortality.

Comparison 5. Amino acid solution, alone or in combination with dextrose, compared to dextrose solution

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications	2	104	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.32, 1.82]
2 Length of hospital stay	2	104	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Mortality	1	60	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 Amino acid solution, alone or in combination with dextrose, compared to dextrose solution, Outcome 1 Complications.

Analysis 5.2. Comparison 5 Amino acid solution, alone or in combination with dextrose, compared to dextrose solution, Outcome 2 Length of hospital stay.

Analysis 5.3. Comparison 5 Amino acid solution, alone or in combination with dextrose, compared to dextrose solution, Outcome 3 Mortality.

Comparison 6. Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Complications	1	61	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.47, 1.13]
2 Length of hospital stay	1	61	Mean Difference (IV, Random, 95% CI)	-0.30 [-3.64, 3.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Mortality	1	61	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.06, 14.78]

Analysis 6.1. Comparison 6 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement, Outcome 1 Complications.

Analysis 6.2. Comparison 6 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement, Outcome 2 Length of hospital stay.

Analysis 6.3. Comparison 6 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement, Outcome 3 Mortality.

ADDITIONAL TABLES

Table 1. Description of interventions

Study	Intervention	Interventions appropriate as applied in a clinical practice setting ^a	Comparator	Comparator appropriate as applied in a clinical practice setting ^a
Hamil-ton-Reeves 2016	I1: immuno-enhancing nutrition supplement drinks 3 cartons daily	Pre- and postoperatively	C1: oral nutrition supplement drink 3 cartons a day	5 days pre- and 5 days postoperatively
Deibert 2016	I1: clear fluid diet and access to full diet on day 2	Postoperatively	C1: standard postoperative care	From day 1 postoperatively
Ritch 2018	I1: oral nutritional supplements (Ensure Clinical Strength)	Pre and postoperatively	C1: oral multivitamin and mineral supplement	3–4 weeks pre- and 4 weeks postoperative
Roth 2013	I1: parenteral nutrition 1500 mL/day (1860 kcal, 150 g AA, 360 g glucose)	Postoperatively	C1: oral nutrition with Ringer's lactate solution with additional potassium 1500 mL/24 hours	For 5 days postoperatively
Rovera 1989	I1: oral nutritional supplements (Precision N, 30 kcal/kg/day, 1.5 g protein/kg/day)	10 days preoperatively	C1: normal diet up to surgery	Normal diet up to surgery
Bonau 1984	I1: AA solution containing 25% branch chain (30 kcal/kg/day, 1.5 g of protein/kg/day) I2: AA solution with 45% branch chain AA (30 kcal/kg/day, 1.5 g of protein/kg/day)	Started postoperative day 1 and stopped postoperative day 8	C1: dextrose 150 g in 3 L of water (intravenously administered over 24 hours)	Infusions started at postoperative day 1 and stopped at postoperative day 8
Daly 1982	I1: AA solution containing (1.3–1.5 g/kg/day) I2: intravenous fluids containing dextrose and AA (1.3–1.5 g/kg/day)	3 days preoperatively until a minimum of 7 days postoperatively	C1: dextrose (intravenously administered)	3 days preoperatively until a minimum of 7 days postoperatively
Hensle 1978	I1: AA 0.7–1.0 g/kg/day and calories 240 kcal/day	Postoperative Duration NR	C1: 5% dextrose	Postoperative Duration NR

^aThe term 'clinical practice setting' refers to the specification of the intervention/comparator as used in the course of a standard medical treatment (such as dose, dose escalation, dosing scheme, provision for contraindications and other important features).

AA: amino acid; C: comparator; I: intervention; N/CPS: no specification of clinical practice setting possible; NR: not reported.

Table 2. Baseline characteristics

Study	Intervention and comparator	Duration of intervention and follow-up	Trial period	Country	Setting	Ethnic groups
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Table 2. Baseline characteristics (Continued)

Hamil-ton-Reeves 2016	I1: immuno-enhancing nutrition supplement	5 days pre- and 5 days postoperatively	2013–2015	USA	Home and hospital	—
	C1: oral nutrition supplement	Follow-up for 90 days postoperatively				—
Ritch 2018	I1: oral nutritional supplements	Follow-up for 30 days postoperatively	April 2014–December 2016	USA	Home and hospital	—
	C1: multivitamin and mineral supplements					
Deibert 2016	C1: normal diet	Duration NR Follow-up for 90 day postoperative	2011–2014	USA	Hospital	74% white, 8% black, 4% Hispanic, 8% other
	C1: standard postoperative care					76% white, 9.8% black, 6% Hispanic, 8% other
Roth 2013	I1: parenteral nutrition	5 days postoperatively	2008–2011	Switzerland	Hospital	—
	C1: oral nutrition with Ringer's lactate solution	Follow-up for 30 days postoperatively				—
Rovera 1989	I1: oral nutritional supplements	10 days preoperatively	—	Italy	—	—
	C1: normal diet	Follow-up 30 days post-operatively				—
Bonau 1984	I1: AA solution with 25% branch chain AA	From postoperative days 1–8	—	USA	Hospital	—
	I2: AA solution with 45% branch chain AA	Follow-up NR				—
	C1: dextrose					—
Hensle 1978	I1: intravenous fluids containing dextrose and AA	Duration NR Follow-up 60 days	—	USA	Hospital	—
	C1: 5% dextrose					—

AA: amino acid; C: comparator; I: intervention; NR: not reported.

APPENDICES

Appendix 1. Evidence Based Medicine Reviews (Ovid) search strategy

1. bladder cancer.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
2. (bladder* cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma*).mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
3. cystectomy.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]

4. NUTRITIONAL STATUS.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
5. Food.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
6. immune enhancing nutrition.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
7. NUTRITIONAL SUPPORT.mp. [mp=ti, ot, ab, tx, kw, ct, sh, hw]
8. 1 or 2
9. 4 or 5 or 6 or 7
10. 3 and 8 and 9

Appendix 2. MEDLINE (Ovid) search strategy

1. exp BLADDER NEOPLASMS/
2. ((bladder*) adj5 (cancer* OR tumour* OR tumour* OR neoplas* OR malignant* OR carcinoma*)).mp
3. 1 OR 2
4. exp PERIOPERATIVE CARE/
5. exp PERIOPERATIVE PERIOD/
6. (peri-operative OR perioperative).mp
7. ((cystect*) adj5 (rad* OR total*)).mp
8. exp CYSTECTOMY/
9. 4 OR 5 OR 6 OR 7 OR 8
10. exp NUTRITIONAL SUPPORT/
- 11 exp NUTRITIONAL STATUS/
- 12 exp NUTRITION THERAPY/
- 13 exp NUTRITION ASSESSMENT/
- 14 exp CACHEXIA/
- 15 exp MALNUTRITION/
- 16 exp BODY WEIGHT/
- 17 exp WEIGHT LOSS/
- 18 exp THINNESS/
- 19 (weight OR underweight OR weight loss OR thinness OR cachexia OR malnutrition).mp
- 20 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19
- 21 exp FOOD/
- 22 exp FOOD, FORMULATED/
- 23 exp VITAMINS/
- 24 exp MICRONUTRIENTS/
- 25 (nutrition* OR nutrient* OR macronutrient* OR micronutrient* OR immuno nutrition OR immuno-nutrition).mp
- 26 exp DIET/
- 27 diet.mp

28 exp DIET THERAPY/
29 exp AMINO ACIDS/
30 exp FATTY ACIDS/
31 exp FATTY ACIDS, Omega-3/
32 exp FISH OILS
33 exp GLUTAMINE
34 exp ARGININE/
35 exp NITROGEN
36 novel AND substrate*.mp
37 (diet therap* OR amino acid* OR fatty acid* OR fish oil* OR glutamine*).mp
38 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR
36 OR 37
39 exp FEEDING METHODS/
40 exp ENTERAL NUTRITION/
41 exp PARENTERAL NUTRITION/
42 exp PARENTERAL NUTRITION, TOTAL/
43 exp GASTROSTOMY/
44 exp JEJUNOSTOMY/
45 (enteral OR parenteral OR TPN OR naso-gastric OR nasogastric OR gastrostomy OR jejunostomy OR hyperalimentation).mp
46 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45
47 20 OR 38 OR 46
48 randomized AND controlled AND trial.pt.
49. controlled AND clinical AND trial.pt.
50. randomized.ab.
51 placebo.ab.
52 clinical AND trials AND as AND topic.sh.
53. trial.ti.
54 48 OR 49 OR 50 OR 51 OR 52 OR 53
55 3 AND 9 AND 47 AND 54
56 exp ANIMALS/ NOT humans.sh
55 NOT 56

Appendix 3. Embase (Ovid) search strategy

1 EXP BLADDER TUMOR/
2 (bladder* adj3 (cancer* or tumo?r* or neoplas* or malignan* or carcinoma*)).mp
3 1 or 2

4 PERIOPERATIVE PERIOD/

5 (peri-operative or perioperative).mp.

6 EXP BLADDER SURGERY/

7 EXP CYSTECTOMY/

8 (cystectom* or cystostom* or cytostom* or ureteroneocystectom*).mp.

9 or/4-8

10 EXP NUTRITIONAL SUPPORT/

11 EXP NUTRITIONAL STATUS/

12 EXP DIET THERAPY/

13 EXP NUTRITIONAL ASSESSMENT/

14 EXP MALNUTRITION/

15 EXP CACHEXIA/

16 EXP BODY WEIGHT/

17 / EXP WEIGHT REDUCTION

18 EXP FOOD/

19 EXP FOOD INTAKE/

20 EXP NUTRITION/

21 EXP PARENTERAL NUTRITION/

22 EXP ENTERIC FEEDING/

23 EXP NOSE FEEDING/

24 EXP GASTROSTOMY/

25 EXP JEJUNOSTOMY/

26 EXP FISH OIL/

27 EXP AMINO ACID/

28 EXP FATTY ACIDS/

29 EXP OMEGA 3 FATTY ACID/

30 EXP GLUTAMINE/

31 EXP ARGININE/

32 EXP NITROGEN/

33 EXP TRACE ELEMENTS/

34 EXP VITAMIN/

35 (weight or underweight or thinness or cachexia or malnutrition).mp.

36 (nutrition* or nutrient* or macronutrient* or micronutrient* or immunonutrition or immuno-nutrition).mp.

37 (food* or feed* or supplement* or vitamin* or mineral* or protein* or fat* or carbohydrate* or calorie*).mp.

38 (amino acid* or fatty acid* or fish oil* or "omega 3" or glutamin* or arginine).mp.

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy (Review)

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- 39 (enteral or parenteral or TPN or naso-gastric or nasogastric or gastrostomy or jejunostomy).mp.
 40 (novel adj2 substrat*).tw.
 41 or/10-40
 42 3 and 9 and 41
 43 CROSSOVER PROCEDURE/
 44 DOUBLE-BLIND PROCEDURE/
 45 RANDOMIZED CONTROLLED TRIAL/
 46 SINGLE-BLIND PROCEDURE/
 47 (random\$ or factorial\$ or crossover\$ or cross over\$ or placebo\$ or assign\$ or allocat\$ or volunteer\$).mp.
 48 ((doubl\$ or singl\$) adj blind\$).mp.
 49 or/43-48
 50 42 and 49

Appendix 4. AMED (Ovid) search strategy

- 1 exp BLADDER NEOPLASMS/
 2 (bladder* cancer* or tumor* or tumour* or neoplas* or malignan* or carcinoma*).mp. [mp=abstract, heading words, title]
 3 1 or 2
 4 exp humans/ or exp Surgery/ or surgical*.mp.
 5 3 and 4
 6 exp Nutritional status/ or exp Therapy/ or exp Nutrition/ or NUTRITIONAL SUPPORT.mp. or Neoplasms/
 7 Nutrition therapy/ or NUTRITION THERAPY.mp.
 8 Diet/ or Nutrition/ or Metabolism/ or NUTRITION ASSESSMENT.mp. or Diet therapy/
 9 exp cachexia/ or CACHEXIA.mp.
 10 Body weight/ or BODY WEIGHT.mp.
 11 Weight loss/ or WEIGHT LOSS.mp.
 12 THINNESS.mp. or Body image/
 13 6 or 7 or 8 or 9 or 10 or 11 or 12
 14 Dietary supplements/ or Food/ or Diet/ or Food.mp.
 15 FOOD, FORMULATED.mp. or Food/
 16 exp Nutrition/ or exp Vitamins/ or VITAMINS.mp.
 17 Nutrition/ or exp Vitamins/ or MICRONUTRIENTS.mp. or exp Minerals/ or Diet/
 18 DIET.mp. or exp Diet/ or exp Vitamins/
 19 exp Nutrition/ or exp Diet therapy/ or DIET THERAPY.mp.
 20 Dietary supplements/ or exp Amino acids/ or exp Nutrition/ or AMINO ACIDS.mp.
 21 FATTY ACIDS/
 22 humans/ or Fatty acids/ or FATTY ACIDS, Omega-3.mp.

23 exp Fish oils/ or Diet therapy/ or FISH OILS.mp.

24 Metabolism/ or exp Amino acids/ or GLUTAMINE.mp.

25 Postoperative complications/ or Surgery operative/ or exp Enteral feeding/ or Nutrition disorders/ or JEJUNOSTOMY.mp.

26 humans/ or Amino acids/ or ARGININE.mp. or exp Dietary supplements/

27 exp Nitrogen/ or exp Muscle physiology/ or nitrogen.mp.

28 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27

29 Gastrostomy/ or exp Feeding methods/ or FEEDING METHODS.mp.

30 Food/ or Enteral feeding/ or enteral.mp.

31 Parenteral feeding/ or Therapy/ or parenteral.mp.

32 Gastrostomy/ or GASTROSTOMY.mp. or Enteral feeding/

33 exp Enteral feeding/ or JEJUNOSTOMY.mp.

34 29 or 30 or 31 or 32 or 33

35 28 or 34

36 randomised controlled trial.mp. or exp Randomized controlled trials/

37 trial.mp. or exp Clinical trials/ or exp Randomized controlled trials/

38 36 or 37

39 13 or 35

40 3 and 5 and 38 and 39

41 limit 40 to yr="2012 -Current"

Appendix 5. CINAHL (Ebsco) search strategy

Search terms used were 'cystectomy', 'nutrition', 'diet'; these were combined to run the search.

Appendix 6. mRCT search strategy

Search terms: bladder cancer, nutrition

Appendix 7. NCI search strategy

Search terms: bladder cancer, supportive therapy, nutrition all stages of trials.

Appendix 8. ClinicalTrials.gov search strategy

Search terms: bladder cancer, nutrition

Appendix 9. WHO ICTRP search strategy

Search terms: bladder cancer, nutrition

Appendix 10. Zetoc search strategy

Search terms: bladder cancer, nutrition

Appendix 11. WorldCatDissertations search strategy

Search terms: bladder cancer and nutrition

CONTRIBUTIONS OF AUTHORS

HAB and SB wrote the protocol.

SB and HAB wrote the review.

SB and HAB completed the analysis and the 'Summary of findings' tables.

KO, HAB and SB reviewed titles for included studies.

AM provided expert surgical knowledge regarding the interpreting of the studies.

SL provided expert knowledge on clinical nutrition and all authors contributed to the script.

DECLARATIONS OF INTEREST

SB: received a Macmillan Post Doctoral Fellowship Award for postdoctoral research, which was paid to her institution and unrelated to this work.

HAB: the author's institution, Central Manchester University Hospitals NHS Foundation Trust (CMFT) receives some funds in association with enteral feed procurement from Nutricia Ltd who have had no involvement with this Review.

SL: received honoraria and educational support from Baxter, B Braun and Fresenius Kabi which was unrelated to this work.

KAO: the author's institution, Central Manchester University Hospitals NHS Foundation Trust (CMFT) receives some funds in association with enteral feed procurement from Nutricia Ltd who have had no involvement with this review.

AM: received honoraria and educational support from Eli Lilly and Bayer.

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All authors work in the NHS and receive salaries from the NHS

External sources

- Macmillan Cancer Care, UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review was based on a published protocol ([Burden 2012b](#)), with differences as described here.

- Nutrition measures and biochemistry markers were listed as a secondary outcome but were excluded from the review based on guidance from the editorial group to focus on patient-important outcomes.
- In the protocol, searches were to include CRG's Specialised Register, CENTRAL, BNI, DARE and Physicians Data Query; however, instead we searched Evidence Based Medicine. This change was due to the availability of databases changing over time and the Evidence Based Medicine became available and was considered a more appropriate option for this topic. We were unable to access the OCLC WorldCat Dissertations and Theses website after December 2014 due to changes in the website. We did not search the CRG's Specialised Register due to the transfer of this review from the Renal to the Urology Group.
- In the Methods section 'Types of studies', we clarified that quasi-RCTs were eligible for inclusion, for consistency with the 'Unit of analysis issues' section.
- We added for clarification, "studies where a nutritional intervention was included in a package of care have been excluded" to methods section.
- In the Methods section 'Search methods for identification of studies', we clarified that the search methods did not utilise restrictions based on language of publication or publication status.
- We updated methods to correspond to current MECIR and editorial group standards at the time of publication. This included the use of GRADE on a per-outcome basis ([Schünemann 2011](#)).

NOTES

Parts of the Methods section of this review were based on a standard template developed by the Cochrane Metabolic and Endocrine Disorders Group that has been modified and adapted for use by the Cochrane Urology Group.

INDEX TERMS

Medical Subject Headings (MeSH)

*Perioperative Care; Cystectomy [*methods]; Length of Stay; Nutritional Status; Postoperative Complications [*epidemiology]; Urinary Bladder Neoplasms [*surgery]; Wound Healing

MeSH check words

Humans