Perioperative nutrition for the treatment of bladder cancer by radical cystectomy

DOI:
10.1002/14651858.CD010127.pub2

Document Version
Accepted author manuscript

Perioperative nutrition for the treatment of bladder cancer by radical cystectomy

Review information

Review type: Intervention

Authors

Sorrel Burden[1], Hazel A Billson[2], Simon Lal[3], Kellie A Owen[2], Asif Muneer[4]

[1]School of Health Sciences, The University of Manchester, and Manchester Academic Health Science Centre, Manchester, UK
[2]Dietetic Department, Platt 2 Rehabilitation, Manchester Royal Infirmary, Manchester, UK
[3]Intestinal Failure Unit, Salford Royal Foundation Trust, Salford, UK
[4]Department of Urology and NIHR Biomedical Research Centre, University College London Hospital, London, UK

Citation example: Burden S, Billson HA, Lal S, Owen KA, Muneer A. Perioperative nutrition for the treatment of bladder cancer by radical cystectomy. Cochrane Database of Systematic Reviews 2012 , Issue 11 . Art. No.: CD010127. DOI: 10.1002/14651858.CD010127 .

Contact person

Hazel A Billson

Research Dietitian
Dietetic Department, Platt 2 Rehabilitation
Manchester Royal Infirmary
Oxford Road
Manchester
M13 9WL
UK

E-mail: Hazel@billson.org
E-mail 2: Hazel.Billson@cmft.nhs.uk

Dates

Assessed as Up-to-date:	30 June 2018
Date of Search:	30 June 2018
Next Stage Expected:	28 December 2020
Protocol First Published:	Issue 11 , 2012
Review First Published:	Not specified
Last Citation Issue:	Issue 11 , 2012

What's new

Date	Event	Description

History

Date	Event	Description

Abstract

Background

Radical cystectomy (RC) is the primary surgical treatment for muscle-invasive urothelial carcinoma of the bladder. This major operation is associated with an extended hospital stay, a prolonged recovery period and major complications. Nutritional interventions have been shown to be 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 participants 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 June 30, 2018, 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 at each stage and undertook data extraction and risk of bias and GRADE assessments of the quality of evidence. Primary outcomes were postoperative complications at 90 days and length of hospital stay. 90 -day Mortality was the predefined secondary outcome. When 90 day outcome data was not available, we reported 30 day data.

Main results

Eight trials were identified 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% CI (confidence intervals) 1.07 to 1.82; low quality of evidence). We downgraded for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious imprecision. This correspond to 198 more complications per 1000 participants (95% CI 35 more to 405 more). Length of stay may be similar (mean difference (MD) 0.5 days higher; no CI reported, low quality of evidence). We downgraded for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious imprecision.

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 of evidence). These findings correspond to 322 fewer complications per 1000 participants; 95% CI 429 fewer to 107 more). Length of stay may be similar (MD 0.20 days, 95% CI 1.69 lower to 2.09 higher; low quality of evidence). We downgraded 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 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 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 of evidence) but we are very uncertain of this finding. We downgraded for serious study limitations (unclear risk of selection and performance bias) and very serious imprecision. Length of stay may be similar (MD: 0.95 days less; no CI reported, low quality of evidence). We downgraded for serious study limitations (unclear risk of selection and performance bias) and serious imprecision.

5. Amino acid alone with dextrose versus dextrose: based on two studies with 104 participants, we are very uncertain whether amino acids reduce postoperative complications (very low quality of evidence). We are also very uncertain whether length of stay is similar (very low quality of evidence). We downgraded 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 of evidence). We downgraded 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 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 of evidence). These findings correspond 135 fewer occurrences per 1000 participants (95% CI 256 fewer to 65 more)**.** Length of stay may be similar (low quality of evidence). We downgraded 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 of patients 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 with a possibility of becoming 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 30 June 2018. There were eight studies conducted including 500 people in hospital. There were seven different ways in which nutrition was given.

Key Results

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

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 including 29 people. We found that IE nutrition may decrease complications 90 days after surgery but may have little effect on LoHS.

3. Preoperative oral nutrition support versus diet: based on one study including 28 people we are uncertain if oral supplements before surgery improves complications after surgery. LoHS was not reported.

4. Early postoperative feeding versus standard care: based on one study with 102 people early postoperative feeding may increase postoperative complications after surgery but we are very uncertain of this finding. LoHS may be similar.

5. Amino acids versus dextrose: Amino acids are the building blocks of proteins and dextrose is sugary water. From two studies with 104 people we are uncertain whether complications may be reduced and LoHS may be similar.

6. Branch chain versus dextrose: Branch chain are a type of amino acid. From one study with 19 people we are uncertain whether complication rates are similar. LoHS was not reported.

7. Perioperative oral nutritional supplements versus multivitamin and mineral supplement: From one study with 61 participants, oral supplements compared to a multivitamin and mineral supplement may slight decrease postoperative complications and LoHS stay may be similar.

Quality of the evidence

The quality of the evidence in this review was low or very low.

Background

Description of the condition

The worldwide incidence of bladder cancer is reported to be 5.3 per 100,000 people (age-standardized 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%) (Braud 2002; Tobias 2010) 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). The standard treatment for this is transurethral resection of bladder tumour (TURBT), 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 (TCC). 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 (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, vagina, or become fixed to the pelvic side wall. Invasive bladder cancer is associated with a greatly increased mortality rate in comparison with 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 (CIS).

Radical cystectomy is a major surgical procedure consisting of the removal of the bladder together with the prostate and seminal vesicles in males, or the bladder and urethra together with the anterior vaginal wall and uterus in females. 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 patients, 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 United Kingdom 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 (South West Public Health Observatory 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 co-morbidities, 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 side 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 a 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 grams per day, which was significantly higher than among those who were tube fed into the jejunum (Daly 1987).

Nutritional status is considered an important factor in determining postoperative outcomes in RC (Giulia 2017) and a number of 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 those with urological cancers (including 40% with bladder cancer) were found to have a high nutrition risk score (Karl 2009). In a survey of 277 urologists in the United Kingdom, the proportion of inadequately nourished people admitted for RC was estimated to be 23% (Barrass 2006). Although a high incidence of obesity in people undergoing RC in the United States has been recorded (26% of 1142) (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 reduced complications postoperatively were demonstrated 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 side 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 blood stream infections.

How the intervention might work

Malnutrition has been linked to complications following RC. Thirteen out of 33 people (39%) undergoing RC in an American 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 (HR) 2.91, 95% confidence interval (CI) 1.36 to 6.23, (P ? 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 stay were old age, American Association of Anaesthetists (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 significant weight loss greater than 10% in the previous six months was observed in 5.4% of people and was associated with increased mortality at 30 and 90 days odds ratio (OR) 2.7, 95% CI 1.1 to 6.4, and OR 2.9, 95% CI 1.5 to 5.4, respectively, this factor may also be amenable to pre-operative nutrition intervention (Hollenbeck 2006).

The use of nutrition supplements pre-operatively 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 (18.5%) used PN or (6.5%) enteral nutrition routinely, although a larger proportion (29%) felt 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 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 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 those 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 and concluded that there may be a reduction in complication rates but not death rates for those receiving PN (Heyland 2001).

More recently a variety of nutrition strategies have been employed on multimodal programmes for people undergoing RC (Maffezzini 2006, Azhar 2016). 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 minimize 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). A significantly reduced hospital stay was also noted in Bristol (UK), where clear fluids were introduced¬in recovery and light diet was permitted from day two postoperatively, or nasogastric (NG) 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 patients 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 aim 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 provided at any stage in the perioperative period during which RC was undertaken as a treatment for bladder cancer. Nutritional interventions could be one or more of the following: additional food or drink, fortified foods, oral supplements, and enteral or parenteral feeds. Nutritional products could be supplementary to the usual food and drink or could be 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 have been excluded.

Comparisons which include any nutritional interventions with 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 have 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 was available, we reported those figures.

Types of outcome measures

Primary outcomes

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

For length of 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 until 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)
- WHO ICTRP (www.who-int/ictrp/; see Appendix 9)

We searched meeting abstracts through the following web sites to June 2017.

- Zetoc (zetoc.mimas.ac.uk; see Appendix 10)
- OCLC WorldCat Dissertations and Theses (WorldCatDissertations) www.oclc.org/support/services/firstsearch/documentation/dbdetails/details/WorldCatDissertations.en.html; see Appendix 11)

We carried out translations, when needed.

Searching other resources

Where ongoing trials were identified, attempts were made to contact principal investigators to ask for 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

Titles and abstracts retrieved by the searches were downloaded and groups of two review authors (HAB, SB, and KO) independently assessed these to determine relevance and eligibility. The full article was obtained 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 have been included. Where the same outcomes are reported, the latest study has been included with the longest follow up.

Data extraction and management

A data collection form was devised which was piloted and modified. Two review authors (HAB and SB) undertook the process of data extraction independently with discrepancies discussed between themselves or, where translation was required, one of these review authors worked with a translator. Each trial was examined for 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.

We extracted outcomes data as below:

For dichotomous outcomes, 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, 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 The Cochrane Collaboration's 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 a 'Risk of bias graph' figure and a 'Risk of bias summary' figure.

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), the risk of bias was evaluated separately for each outcome, and outcomes were grouped according to whether measured subjectively or objectively.

The following endpoints were defined as subjective outcomes for performance bias (blinding of participants and personnel)

- Complications
- Length of stay

The following endpoint was defined 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 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, the risk ratio (RR) with 95% confidence interval (CI) was used, and for continuous outcomes, the mean difference (MD) with 95% CI.

Unit of analysis issues

- Trials that were cluster-randomised were planned to be considered 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 it was 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

Heterogeneity between studies was assessed 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 per cent 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

Multiple sources were searched as detailed above. 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, the random effects model was used. Statistical analyses were conducted according to the guidelines in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). For dichotomous outcomes, the Mantel-Haenszel method was used 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

Subgroup analyses were not undertaken due to the lack of suitable data, planned sub-group analysis was to group the trials according to:

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

In the interpretation of any heterogeneity, baseline characteristics including factors of age (< 70 years and ? 70 years), cancer staging, type of nutrition intervention (oral, enteral, parenteral), length of follow up (one month, three months) were considered.

Sensitivity analysis

If six or more studies had been suitable for meta-analysis in this review, sensitivity analyses would have been conducted 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' table

The overall quality 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 also to external validity (directness of results) (Guyatt 2008). For each comparison, two authors (SB, HB) independently rated the quality of evidence for each outcome as 'high', 'moderate', 'low', or 'very low', and resolved discrepancies by discussion. GRADEpro GDT was used to prepare a summary of the evidence for the primary outcomes in a 'Summary of findings' table 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.

Results of the search

See Figure 1. From searches and updated searches run on the electronic databases to 30 June 2018, 5514 titles were identified; after scanning titles and reviewing abstracts we obtained 16 full reports describing relevant studies plus a further study was identified in a conference abstract and one study was published from an ongoing trial. Translation of four reports was undertaken. Of the 18 studies, eight met the inclusion criteria for this review and ten studies were excluded. No quasi-RCTs were identified.

Included studies

See Characteristics of included studies. In the eight studies which met the inclusion criteria for this review 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 (Bonau 1984; Deibert 2016: Hamilton-Reeves 2016; Ritch, 2018;Roth 2013; Rovera 1989), there were 341 males and 82 females; only males were recruited by Bonau 1984 and Hamilton-Reeves 2016. Five of the studies described the age of the participants who had group mean or median ages of between 61 to 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 was supported by Abbott Laboratories (Bonau 1984), one study was supported by an educational grant from McGaw Laboratories (Hensle 1978), one study was supported by the American Cancer Society, Nestle Healthcare, and travel funding (Hamilton-Reeves 2016); one study received support from Vanderbilt CTSA, NIH National Centre and Abbort Nutrition Award (Ritch, 2018), two studies received no funding (Roth 2013; Deibert 2016); for the remaining two studies there was no disclosure of funding sources (Daly 1982; Rovera 1989).

Two included studies conducted in the USA (134 participants) evaluated the use of amino acid solutions with and without dextrose compared to dextrose solution in the postoperative management of patients following RC (Daly 1982; Hensle 1978). In the study by Daly 1982 93 participants were randomised into 3 arms, although only two arms are included in the analysis with 60 participants comparing amino acid solution with dextrose to dextrose solution as the control. One study (19 participants) in the USA compared two different branched chain amino acid (BCAA) solutions to dextrose solution (Bonau 1984). In this study (Bonau 1984) there were a total of four arms although only two arms were suitable to be included in this review including 10 participants. A 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 also investigated PN including 157 participants conducted in Switzerland and evaluated PN postoperatively compared to oral diet (Roth 2013). A recent study with 29 participants compared immuno-enhancing nutrition supplements and standard oral nutritional supplements given for 5 days before and 5 days after RC surgery (Hamilton-Reeves 2016). A further study 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, this study included 102 participants (Deibert 2016). One study compared oral nutritional supplements administered 3-4 weeks pre and 4 weeks postoperative to oral multivitamin and mineral supplement, this study included 61 participants (Ritch, 2018).

Excluded studies

See Characteristics of excluded studies. Ten studies were excluded from the review (Brodner 2001; Daly 1987; de Vries 2012; Hensle 1985; Karl 2009, Malossini 1987; Mangano 1993; McArdle 1986; Olbert 2009; Solomon 1978). There were six studies that were excluded as they did not randomise participants, two studies excluded as they did not include a nutritional intervention, one study excluded where there were insufficient RC participants included and one study was excluded as they did not fully meet the inclusion criteria.

Ongoing studies

See Characteristics of ongoing studies. We classified three studies as ongoing studies (NCTO2238886, NCT03204266 and NCT03147586). One of these studies is being undertaken in the USA ((NCT03204266), one in Denmark (NCTO2238886) and one in Egypt NCT03147586.

Risk of bias in included studies

The risk of bias in the included studies is summarised in Figure 2 and displayed graphically in Figure 3.

Allocation (selection bias)

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) and 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 noted 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 included studies 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 (performance bias and detection bias)

Blinding of participants and personnel

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

For subjective outcomes (complications and length of stay) the risk of bias was assessed as low in one study (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: A low risk of bias was detected in two studies (Hamilton-Reeves 2016; Roth 2013) and a unclear risk of bias was detected for this outcome in six studies (Bonau 1984; Daly 1982; Deibert 2016; Hensle 1978; Ritch, 2018: Rovera 1989)

Outcome - length of stay: A low risk of bias was detected in eight studies (Bonau 1984; Daly 1982: Deibert 2016; Hensle 1978; Hamilton-Reeves 2016; Ritch, 2018; Roth 2013; Rovera 1989).

Outcome - mortality: A low risk of bias was detected for this outcome in eight studies (Daly 1982:Bonau 1984; Deibert 2016; Hamilton-Reeves 2016; Hensle 1978; Ritch, 2018; Roth 2013; Rovera 1989).

Incomplete outcome data (attrition bias)

Outcome - complications: An unclear risk of bias was detected in one study (Bonau 1984); a low risk of bias was detected in seven studies (Daly 1982; Deibert 2016; Hamilton-Reeves 2016; Hensle 1978; Ritch, 2018; Roth 2013; Rovera 1989).

Outcome - length of stay: A low risk of bias was detected in six studies (Deibert 2016; Daly 1982; Hamilton-Reeves 2016; Hensle 1978; Ritch, 2018; Roth 2013; Rovera 1989), and an unclear risk of bias was assessed in two studies.(Bonau 1984; Rovera 1989).

Outcome - mortality: A low risk of bias was detected in all eight studies (Bonau 1984; Daly 1982; Deibert 2016; Hamilton-Reeves 2016; Hensle 1978; Ritch, 2018; Roth 2013; Rovera 1989).

Selective reporting (reporting bias)

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

Other potential sources of bias

A low risk for other sources of bias was reported for all studies.

A description of the interventions are shown in Table 1 and baseline characteristics are shown in Table 2.

Effects of interventions

Comparison 1: Postoperative parenteral nutrition compared to oral nutrition

We found one study (Roth 2013), including a total of 157 participants (74 PN, 83 control) that compared postoperative PN to oral nutrition alone.

Summary of findings table 1

Primary outcomes

Postoperative complications

Based on one study with 157 participants, PN may increase postoperative complications within 30 days (risk ratio (RR) 1.40, 95% CI (confidence intervals) 1.07 to 1.82; low quality of evidence) (Analysis 1.1; Figure 4). We downgraded 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% (Roth 2013), this corresponds to 198 more complications

per 1000 participants (95% CI 35 more to 405 more). Length of stay may be similar (mean difference (MD) 0.5 days higher; no CI reported, low quality of evidence). We downgraded for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious imprecision. This study was discontinued prematurely due to more complications occurring in the PN group.

Length of stay

Length of stay may be similar (mean difference (MD) 0.5 days higher; no CI reported, low quality of evidence). We downgraded for serious study limitations (unclear risk of selection, performance and selective reporting bias) and serious imprecision. Length of 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 are very uncertain of the effect of parenteral nutrition compared to oral diet on postoperative mortality rates (RR 1.12, 95% CI 0.07 to 17.62) (Analysis 1.2; Figure 5). The quality of evidence was assessed as very low for this outcome, downgrading 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% (Roth 2013), PN may result in 1 more deaths 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 a total of 29 participants (Hamilton-Reeves 2016), 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.

Summary of findings table 2

Primary Outcomes

Postoperative Complications

Immuno-enhancing nutrition may improve rates of 90 day postoperative complications compared to usual diet group (RR 0.31, 95% CI 0.08 to 1.23; Analysis 2.1: Figure 6). The quality of evidence was graded as low, downgrading two levels for very serious imprecision. Assuming a baseline risk of postoperative complications of 46% (Hamilton-Reeves 2016) immuno-enhancing nutrition may result 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 report for consistency sake given that is was the most prevalently reported time-frame for the outcome of complications for other comparisons. Immuno-enhancing nutrition versus usual care may have little or no effect on rates of 30 day postoperative complications (RR 0.97, 95% CI 0.62 to 1.53; Analysis 2.2: Figure 7). The quality of evidence was graded as low, downgrading two levels for imprecision. Assuming a baseline risk of postoperative complications of 66% (Hamilton-Reeves 2016) immuno-enhancing nutrition would result in 20 fewer occurrences per 1000 participants (95% CI 253 fewer to 353 more).

Length of stay

Length of stay may be similar (MD 0.20 days, 95% CI 1.69 lower to 2.09 higher; low quality of evidence; Analysis 2.3; Figure 8). We downgraded the quality of evidence for very serious imprecision.

Secondary outcomes

Mortality

Immuno-enhancing nutrition compared to standard may have little or no effect on mortality rates (RR approximately 1; 95% CI not reported; low quality evidence) There were no deaths reported in the period up to 90 days post-operatively. The quality of evidence for this outcome was assessed as low, downgrading by two levels for assumed very serious imprecision. No absolute effect size estimates for the confidence intervals could be generated.

Comparison 3: Preoperative oral nutritional support compared to normal diet

We found one study including a total of 28 participants that compared preoperative oral nutritional support to normal diet (Rovera 1989). Both groups also had postoperative PN.

Summary of findings table 3.

Primary outcomes

Complications

Based on one study including 28 participants, we are very uncertain if preoperative oral supplements reduces postoperative complications (Analysis 3.1; Figure 9). 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% (Rovera 1989) preoperative nutrition would result in 21 fewer occurrences per 1000 participants (95% CI 154 fewer to 658 more).

Length of stay

This outcome was not reported.

Secondary outcomes

Mortality

We are uncertain whether preoperative oral nutrition compared to standard care has any effect on mortality rates (RR 1, 95% CI not reported). The quality of evidence was graded as very low, downgrading for study limitations and two levels due to 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 a total of 102 participants (Deibert 2016), 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 in comparison with standard postoperative care where oral intake was delayed until either flatus or a bowel movement had occurred. Follow up was reported for a period of 90 days after surgery.

See Summary of findings table 4. All data for this comparison was obtained from the published report, the authors provided the study protocol for us.

Primary outcomes

Complications

Early postoperative feeding compared to standard care may have little or no effect on postoperative complications (RR 1.14, 95% CI 0.85 to 1.53) (Analysis 4.1; Figure 10). The quality of evidence was graded as low, downgrading for study limitations and imprecision. Assuming a baseline risk of postoperative complications of 59% (Deibert 2016) early postoperative feeding would result in 83 more occurrences per 1000 participants (95% CI 89 fewer to 316 more).

Length of stay

Early postoperative feeding compared to standard care may have little or no effect on length of stay (MD 0.95 days, CI not reported). Quality of evidence was assessed as low, downgrading for study limitations and downgraded one level as 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 little or no effect on postoperative mortality rates (RR 0.52, 95% CI 0.10 to 2.71 Analysis 4.2, Figure 11). The quality of evidence for this outcome was assessed as low, downgraded for study limitations and imprecision. Assuming a baseline risk of postoperative mortality of 3.8% (Deibert 2016) early feeding would result 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 (Daly 1982; Hensle 1978), including a total of 104 participants, that compared an amino acid solution, alone or in combination with dextrose, to dextrose solution.

See Summary of findings table 5.

Primary outcomes

Complications

Two studies (Daly 1982; Hensle 1978), including a total of 104 participants reported complications.

We are uncertain if amino acid solution alone or in combination with dextrose solution has any effect on postoperative complications (RR 0.77, 95% CI 0.32 to 1.82; heterogeneity was I^2 13% applicable) (Analysis 5.1; Figure 12). The quality of evidence was graded as very low, downgrading for study limitations, indirectness as the study used historical methods and imprecision. Assuming a baseline risk of postoperative complications of 20% (Daly 1982) amino acid solution alone or in combination with dextrose solution would result in 46 fewer occurrences per 1000 participants (95% CI 136 fewer to 164 more).

Length of hospital stay

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

We are uncertain if amino acid solution alone or in combination with dextrose solution has any effect on length of stay (MD 0.5 days) (Hensle 1978). Quality of evidence was assessed as very low, downgrading for study limitations, indirectness as the data used historic methods and downgraded one level as study was underpowered to demonstrate a clinically important difference of one day in length of hospital stay.

Secondary outcomes

Mortality

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

We are uncertain if amino acid solution alone or in combination with dextrose solution has any effect on mortality rates (RR 1, 95% CI not reported). The quality of evidence was graded as very low, downgrading for study limitations, indirectness, and there were too few events to reliably assess this outcome so downgraded one level.

Comparison 6: Branched chain amino acids solution and dextrose compared to dextrose only

We found one study including a total of 19 participants (Bonau 1984), that compared branched chain amino acids solution and dextrose to dextrose only.

Summary of findings table 6.

Primary outcomes

Complications

We are uncertain if branch chain amino acids solution and dextrose compared to dextrose had any effect on complication rates (RR 1, 95% CI not reported). The quality of evidence for this outcome was assessed as very low, downgraded for study limitations, indirectness as data used historical methods and there were too few events and a small sample size to adequately assess this outcome. There were no complications reported in either group.

Length of stay

Length of stay was not reported.

Secondary outcomes

Mortality

Mortality was not reported.

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

We found one study including a total of 61 participants (Ritch, 2018), that compared the provision of oral nutritional supplements 3-4 weeks preoperatively and 4 weeks postoperatively to multivitamin and mineral supplement. Follow up was reported for a period of 30 days after surgery.

See Summary of findings table 7 . All data for this comparison was obtained from the published report and the published protocol.

Primary outcomes

Complications

Perioperative oral supplements compared to an oral multivitamin and mineral supplement may slightly decrease postoperative complications (RR 0.73, 95% CI 0.47 to 1.13) (Analysis 7.1 , Figure 13). The quality of evidence was graded as low, downgrading for study limitations and imprecision. Assuming a baseline risk of postoperative complications of 66% (Ritch, 2018) perioperative oral supplement would result in 135 fewer occurrences per 1000 participants (95% CI 256 fewer to 65 more).

Length of stay

Perioperative oral supplements compared to an oral multivitamin and mineral supplement may have little or no effect on length of stay (MD -0.30 95% CI-3.64 to 3.04) days (Analysis 7.2 , Figure 14). Quality of evidence was assessed as low, downgrading for study limitations and downgraded one level as 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 little or no effect on postoperative mortality rates (RR 0.97 95% CI 0.06 to 14.78 Analysis 7.3 , Figure 15). The quality of evidence for this outcome was assessed as low, downgraded for study limitations and imprecision. Assuming a baseline risk of postoperative mortality of 0.03 (Ritch, 2018) early feeding would result in 1 fewer occurrences per 1000 participants (95% CI 31 fewer to 459 more).

Subgroup analysis

This was not performed as the data was insufficient to undertake specific subgroup analyses as outlined in the protocol.

Sensitivity analysis

No sensitivity analysis was performed due to insufficient data.

Discussion

Summary of main results

We identified eight RCT which informed seven separate comparisons including 500 participants with bladder cancer undergoing a 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. Outcomes were measured in included studies from 8 to 90 days (Deibert 2016; Hamilton-Reeves 2016) postoperatively, the majority of studies reported outcomes at 30 days (Hamilton-Reeves 2016; Ritch, 2018; Roth 2013; Rovera 1989).

We found limited evidence that perioperative nutrition improves patient important outcomes. Specifically, immuno-enhancing

nutrition may reduce 90 day complication rates (low quality evidence). Preoperative oral nutrition support and amino acids with dextrose compared to dextrose alone may reduce 30 day complication rates but we are uncertain of both these findings. Parenteral nutrition when compared to oral nutrition may increase complications (low quality evidence) and so may postoperative feeding (very low quality evidence), although we are very uncertain of the latter finding. Oral supplements given in the perioperative period may slight decrease postoperative complications and the evidence was assessed as low. When assessed, length of stay did not appear substantially affected.

Overall completeness and applicability of evidence

This review has 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 have excluded studies where enhanced recovery after surgery (ERAS) has been evaluated since the results of nutritional interventions cannot 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 patients 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 reflect the variety of approaches that have been devised to enhance the nutritional needs of people undergoing surgery.

An 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 (naso-gastric) feeding. One study examined PN and reported complications as an outcome in all participant postoperatively but showed this had an adverse effect on outcome measures (Roth 2013). There were no studies identified that evaluated PN in those 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 at 90 days after surgery but not at 30 days post surgery; the study was a pilot study so with limited applicability without further replication (Hamilton-Reeves 2016). Although a recent 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 are severely limited by the paucity of studies some of which are very old and therefore not directly applicable to today's patient population, radical cystectomy practice and the type of nutritional interventions available today. Interestingly, none of the studies have looked at nutritional status as an inclusions criteria and where nutritional interventions have been successful in other cancer groups (Burden 2017) participants have lost weight or been at risk or malnutrition 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 confidence intervals. 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 seven 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 error 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.

Four studies have been listed as ongoing (see Characteristics of ongoing studies), however one has been 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

No systematic reviews have been identified specifically examining standard nutritional interventions in the perioperative treatment of patients with bladder cancer undergoing a RC other than reviews of studies reporting nutritional intervention as part of an ERAS protocols (Cerantola 2013; Maffezzini 2008; Melnyk 2011). Studies reporting ERAS protocols were not included in this review. Outcomes need to include both clinical outcomes and patient reported outcomes with economic evaluations. One review on immune enhancing nutrition was identified and 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 pre and post operative oral supplements (Hamilton-Reeves 2016). In a review of patients undergoing RC published since the initiation of this Cochrane review, preoperative nutrition optimisation and early post-operative feeding were identified as important components that urologists should incorporate in a package of care for patients 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 stay may not be impacted by any of the nutritional interventions for which we found 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 re-feeding syndrome (a metabolic response to over-feeding 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.

Acknowledgements

We would like to thank Richard Silvioli and Antje Teubner for assistance in translation of papers from Italian and German into English. We would like to thank our dietetic colleague Christel Lyell for assisting with the task of examining titles and abstracts. We would also like to thank library staff at Central Manchester Foundation Trust for assistance with acquiring reports of studies. Asif Muneer acknowledges support from the NIHR BRC University College London Hospitals.

We acknowledge the work of Molly M. Neuberger as former Managing Editor of Cochrane Urology in the preparation of the protocol. We are very grateful to Ted Skorarus, Heidi Silver, Yair Lotan and Jeffrey Holzbeierlein for their critical appraisal of this review as part of the peer review process. We would like to thank Cochrane Urology Managing Editors Alea Miller and Rob Lane as well as Contact Editor Michael Risk for all their help and assistance with this review.`

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, 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

S Burden: Received a Macmillan Post Doctoral Fellowship Award for post doctoral research, which was paid to her institution and unrelated to this work
HA Billson: 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.
S Lal: Received honoraria and educational support from Baxter, B Braun, Fresenius Kabi which was unrelated to this work.
KA Owen: 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.
A Muneer: Received honoraria and educational support from Eli Lilly and Bayer.

Differences between protocol and review

This review is 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 not able to access the OCLC WorldCat Dissertations and Theses web site after December 2014 due to changes in the web siteWe did not search the CRG's Specialised Register due to 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 utilize restrictions based on language of publication or publication status.
- We were unable to conduct any of the preplanned secondary analyses due to lack of suitable data.
- 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)

Published notes

Parts of the Methods section of this review are 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.

Characteristics of studies

Characteristics of included studies

Bonau 1984

Methods	Study design: Parallel group randomised controlled trial Study dates: Not reported Setting: The study was conducted in the Memorial Sloan-Kettering Centre, New York, USA.

Participants	Inclusion criteria: Males with stage I bladder cancer who underwent a radical cystectomy and an ileal conduit diversion. Exclusion criteria: Patients with metastatic disease, cirrhosis, hepatitis, diabetes or renal failure Total number of participants randomly assigned: 19 Age: Range (years) 46-76 Sex: All male 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: Male 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: Male 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: Male Tumour stage/ grade: Not reported Comorbidities: Not reported
Interventions	All groups: Intravenous solutions as detailed below, but containing similar amounts of electrolytes, trace minerals and vitamins. Infusions began at 8am postoperative day 1 and infusions were stopped at postoperative day 8. During the seven day postoperative study period, none of the patients had any oral intake Group 1 (n=4): 150g dextrose in 3 litres 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 kcals/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.

Outcomes	Complications: No patients 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 patients affected. How measured: Not reported Time point measured: Not reported Time point reported: At the end of the postoperative study period (day 8) Length of hospital stay: This outcome was not reported Mortality: This outcome was 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 were reported
Notes	Language of publication: English An additional Group 4 comprising of 6 patients was studied but not included above as this group consisted of consecutive referrals and not randomly assigned patients.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation is reported to have occurred but was not fully described
Allocation concealment (selection bias)	Unclear risk	There was no reported description of allocation concealment
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality was not reported
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding was reported
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Length of stay	Unclear risk	This outcome was not reported
Blinding of outcome assessment (detection bias) Mortality	Low risk	This outcome was not reported
Incomplete outcome data (attrition bias) Complications	Unclear risk	The reporting was unclear and data were not available by group.
Incomplete outcome data (attrition bias) Length of stay	Unclear risk	This outcome was not reported
Incomplete outcome data (attrition bias) Mortality	Unclear risk	This outcome was not reported
Selective reporting (reporting bias)	Unclear risk	No protocol was available.
Other bias	Low risk	No other bias was detected

Daly 1982

Methods	Study design: Parallel group randomised controlled trial Study dates: Not reported Setting: Study was conducted in the Memorial Sloan-Kettering Centre, New York, USA
Participants	Inclusion criteria: Participants undergoing a total cystectomy and ileal loop diversion following preoperative radiotherapy for bladder cancer Exclusion criteria: Not reported Total number of participants randomly assigned: 93 Age: Mean age across the groups was reported to be similar at 61-63 years Sex: Not reported, but described as similar in each group Nutrition status: Mean % ideal body weight was 107-108 although it is unclear if this was at baseline **Group 1: Intravenous dextrose** Number of all participants randomly assigned: 30 Age: Not reported Sex: Not reported Tumour stage/ grade: Not reported Comorbidities: Not reported **Group 2: Intravenous fluids containing amino acids** Number of all participants randomly assigned: 30 Age: Not reported Sex: Not reported Tumour stage/ grade: Not reported Comorbidities: Not reported **Group 3: Intravenous dextrose and amino acids solution** Number of all participants randomly assigned: 30 Age: Not reported Sex: Not reported Tumour stage/ grade: Not reported Comorbidities: Not reported
Interventions	All groups: Interventions were given from 3 days preoperatively until a minimum of 7 days postoperatively Group 1: (n =30) Participants received intravenous dextrose solution Group 2: (n=30) Participants received intravenous fluids containing 1.3-1.5 g/kg/day amino acids Group 3:(n=30) Participants received intravenous dextrose plus 1.3-1.5 g/kg/day amino acids

Outcomes	Complications Unspecified complications were reported in 17%, 18% and 17% respectively of the 3 groups How measured: Not reported Time point measured: Not reported Time point reported: At the end of the study period Length of hospital stay This was reported as being similar in all groups How measured: Not reported Time point measured: Not reported Time point reported: Not reported Mortality: There were no deaths during the study period How measured: Number of deaths Time point measured: Not reported Time point reported: At the end of the study period
Funding sources	The source of funding was not reported
Declarations of interest	No declarations of interest were reported
Notes	Language of publication: English 93 participants cited as the total number randomised to 3 groups with 30 in each group. There are 3 participants unaccounted for in the report. The study was briefly described as the report was a short abstract.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	The process of allocation was not described
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality is not likely to be affected by blinding
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No blinding was described
Blinding of outcome assessment (detection bias) Mortality	Low risk	This outcome is not likely to be affected by blinding
Incomplete outcome data (attrition bias) Complications	Low risk	There were 93 patients randomised and 90 patients reported in the analysis
Incomplete outcome data (attrition bias) Length of stay	Low risk	There were 93 patients randomised and 90 patients reported in the analysis
Incomplete outcome data (attrition bias) Mortality	Low risk	There were 93 patients randomised and 90 patients reported in the analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol was seen for this study.
Other bias	Low risk	No other bias was identified

Deibert 2016

Methods	Study design: Randomised control trial Study dates: From 2011-2014 Setting: 2 large hospitals in USA

Participants	Inclusion criteria: Adult patients undergoing radical cystectomy and urinary diversion for bladder cancer Exclusion criteria: Not reported Total number of participants randomly assigned: 102 Age: This was not reported Sex: Male = 84, female =18 Nutrition status: This was not reported **Group 1: Early feeding group** Number of participants randomly assigned: 50 Age: Not reported Sex: Male, n=37, female, n=13 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: Male, n =47, female, n=5 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 pro-kinetic 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 would be instigated after tube removal. Group 1: (n=50) Early feeding group was 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) Participants received 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 patients had ileus How measured: Defined as more than or equal to 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: This was reported as not significantly different between groups How measured: Number of days Time point measured: Number of days in hospital Time point reported: Not reported Mortality: There were two 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	The source of funding was not described
Declarations of interest	No declarations of interest were reported.
Notes	Language of publication: English This study was terminated before reaching the planned recruitment numbers due to slow accrual of participants.

Risk of bias table

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	The method of allocation was not described
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality is not likely to be affected by blinding
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No blinding was described
Blinding of outcome assessment (detection bias) Mortality	Low risk	This outcome was not likely to be affected by lack of blinding
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised patients were included in the analysis of this outcome
Incomplete outcome data (attrition bias) Length of stay	Low risk	All randomised patients were included in the analysis of this outcome
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised patients were included in the analysis of this outcome
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 was detected

Hamilton-Reeves 2016

Methods	Study design: Randomised control trial Study dates: September 2013 to April 2015 Setting: Hospital, Kansas City, USA

Participants	Inclusion: Patients undergoing radical cystectomy for primary bladder cancer Exclusion: Swallowing difficulties, metastasis, 10% or greater weight loss in previous 6 months, body mass index less than 18.5, viral infection, immune deficiency, gout or relevant food allergies Total number of participants randomly assigned: 29 Age: Not reported Sex: Male Comorbidities Were assessed using the Charlson Comorbidity Index Nutrition status: Assessed using the validated tool, 'Patient-Generated Subjective Global Assessment' (PG-SGA) and body mass index (BMI) was calculated **Group 1: Immuno-nutrition** Number of participants randomly assigned: 14 Age: Mean age (SD) 69.6 (7.1) years Sex: Male Tumour stage/ grade: Ta, n=1, Tis, n=0, T1, n=2, T2, n=11 Comorbidities: Mean index result was 4.9 Nutrition status: Mean BMI 26, mean PG-SGA score 6.7 **Group 2: Oral nutritional supplements** Number of participants randomly assigned: 15 Age: Mean age (SD) 68.1 (8.0) years Sex: Male Tumour stage/ grade: Ta, n=2, Tis, n=2, T1, n=2, T2, - n=7 Comorbidities: Mean index result was 5.1 Nutrition status: Mean BMI 29, mean PG-SGA score 5.5
Interventions	All groups: Nutrition supplements were given for 5 days preoperatively and 5 days postoperatively, the dose was three cartons per day Group 1: Immuno-nutrition supplement drinks Group 2: Oral nutrition supplement drinks
Outcomes	Postoperative complications Measured: graded according to Clavien-Dindo scheme Timepoint measured: less than=30 days and 31-90 days after surgery Timepoint reported: 30 and 90 days after surgery Infection rates Measured: defined by the need for intervention or prescription Timepoint measured: less than =30 and 31-90 days after surgery Timepoint reported: 30 and 90 days after surgery Length of stay Measured: number of days Timepoint measured:up to discharge Timepoint reported: up to discharge Mortality: Measured: number of deaths Timepoint: measured up to 90 days postoperatively Timepoint reported: up to 90 days postoperatively

Funding sources	American Cancer Society Nestle Healthcare Research grant KL2 Scholars Award Nestle HealthCare Nutrition provided the supplement drinks
Declarations of interest	Research funding from Nestle Healthcare and travel support received by Hamilton-Reeves
Notes	Language of publication: English Some data for this study was published in supplementary tables to the published paper

Risk of bias table

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
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 are not likely 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 stay	Low risk	Length of stay is not likely to be affected by blinding
Blinding of outcome assessment (detection bias) Mortality	Low risk	Mortality rates are not likely to be affected by blinding
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised participants were included in the analysis of this outcome
Incomplete outcome data (attrition bias) Length of stay	Low risk	All randomised participants were included in the analysis of this outcome
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised participants were included in the analysis of this outcome
Selective reporting (reporting bias)	Low risk	In the protocol recorded on www.clinicaltrials.gov measurement all outcomes reported in this review were reported.
Other bias	Low risk	No other bias was detected

Hensle 1978

Methods	Study design: Parallel group randomised controlled trial Study dates: Study dates were not reported Setting: Columbia-Presbyterian Medical Centre, New York, USA
Participants	Inclusion criteria: Patients undergoing radical cystectomy and urinary diversion for invasive bladder cancer Exclusion criteria: Patients with renal failure and/or insulin-dependent diabetes Total number of participants randomly assigned: 44 Age: Age was not reported Sex: Sex was not reported Nutrition status: 17 of the participants were defined by the study authors as having 'nutritional depletion' prior to operation **Group I: Fluid management of 5% dextrose solution** Number of all participants randomly assigned: 15 Age: Age was not reported Sex: Sex was not reported Tumour stage/ grade: Not reported Comorbidities: Not reported Nutrition status: 6 patients were nutritionally depleted preoperatively **Group II: Crystalline amino acid solution** Number of all participants randomly assigned: 29 Age: Age was not reported Sex: Sex was not reported Tumour stage/ grade: Not reported Comorbidities: Not reported Nutrition status: 11 patients were nutritionally depleted
Interventions	Both groups: Vitamins and minerals were given with both preparations The duration of the intervention is not described Group I (n=15): Participants in control group received postoperative fluid management of 5% dextrose solution along with balanced electrolytes as well as whole blood and blood byproducts as necessary. Patients were able to begin oral intake as clinical status indicated Group II (n=29): Participants in the intervention group received crystalline amino acid solution containing a 3% mixture of essential and non-essential amino acids with appropriate micronutrient and co-factors designed to deliver 0.7 to 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 patients were able to meet their energy needs orally

Outcomes	Postoperative complications: Were reported as occurring in 33% of the patients in group I and in 17% of patients in Group II How measured: Not reported but included sepsis, wound dehiscence and renal failure Timepoint measured: Not reported Timepoint reported: Not reported Length of stay: In group I ranged between 17 and 66 days with an average of 32 days, in group II it ranged between 16 and 44 days with average of 27 How measured: Number of days in hospital Timepoint measured: Not reported Timepoint reported: Not reported Mortality: There were no deaths in either group. How measured: Number of deaths Timepoint measured: Up to 60 days after surgery Timepoint reported: Nor reported
Funding sources	Supported by a grant from the Medical Department, McGaw Laboratories.
Declarations of interest	Declarations of interest were not reported
Notes	Language of publication: English 30 patients received preoperative radiotherapy. 4 patients in Group I had to be switched to total parenteral nutrition.

Risk of bias table

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 is not likely to affect outcome
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding was described
Blinding of outcome assessment (detection bias) Length of stay	Low risk	No blinding was described
Blinding of outcome assessment (detection bias) Mortality	Low risk	This outcome is not likely to be affected by blinding
Incomplete outcome data (attrition bias) Complications	Low risk	All patients randomised were reported in the analysis
Incomplete outcome data (attrition bias) Length of stay	Low risk	All patients randomised were reported in the analysis
Incomplete outcome data (attrition bias) Mortality	Low risk	All patients randomised were included in the analysis.
Selective reporting (reporting bias)	Unclear risk	No protocol was available.
Other bias	Low risk	No further bias detected

Ritch, 2018

Methods	Study design: Parallel group randomised controlled trial Study dates: April 2014 - December 2016 Setting: Vanderbilt University Medical Centre, USA

Participants	Inclusion criteria: Patients with urothelial carcinoma of the bladder Exclusion criteria: Patients who were not surgical candidates Total number of participants randomly assigned: 61 Age: ≥ 18 years Sex: males n=54 females n=7 Performance status: Eastern Cooperative Oncology Group performance status ≤3 **Group I: Oral nutritional supplements** Number of all participants randomly assigned: 31 Age: 69 +/- 14.1 years Sex: males n=26 females n=5 Tumour stage ≤T1n=14, ≤T2 n=11, ≤T3-T4 n= 6 Comorbidities: Charlson Comorbidity Index 0 n=13, 1 n=7, 2 n=8, ≥ 3 n=3 Nutrition status: Body mass index 27.8 +/-17.9 **Group 2: Multivitamin and minerals** Number of all participants randomly assigned: 30 Age: 66.7 +/-9.6 years Sex: males n=28 females n=2 Tumour stage/ grade: ≤T1 n=17, ≤T2 n=9, ≤T3-T4 n=4 Comorbidities: Charlson Comorbidity Index 0 n=14, 1 n=8, 2 n=4, ≥ n=4 Nutrition status: Body mass index 29.3 +/-5.5
Interventions	Both groups: The intervention was given for 3-4 weeks preoperatively and 4 weeks postoperatively Group I (n=31): Participants in the oral nutritional supplement group received Ensure Clinical Strength, Abbort Nutrition one serving twice daily Group 2 (n=30): Participants in the multivitamin and mineral group received one serving twice daily
Outcomes	Complications How measured: Clavien Dindo classification system Timepoint measured: up to 30 days Timepoint reported: up to 30 days Length of stay: reported in days Mortality: How measured: confirmation of obituary statement Timepoint measured: 30 days Timepoint reported: 30 days
Funding sources	Supported by Vanderbilt CTSA, NIH National Centre and Abbort Nutrition Award
Declarations of interest	Nil stated
Notes	

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation was not described
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Blinding is not likely to affect outcome
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding was reported
Blinding of outcome assessment (detection bias) Complications	Unclear risk	No blinding was reported
Blinding of outcome assessment (detection bias) Length of stay	Low risk	Blinding is not likely to affect outcome
Blinding of outcome assessment (detection bias) Mortality	Low risk	Blinding is not likely to affect outcome
Incomplete outcome data (attrition bias) Complications	Low risk	Eight participants were not included in reporting this outcome one patient died and surgery was aborted and 7 patients withdrew
Incomplete outcome data (attrition bias) Length of stay	Low risk	Eight participants were not included in reporting this outcome one patient died and surgery was aborted and 7 patients withdrew
Incomplete outcome data (attrition bias) Mortality	Low risk	Eight participants were not included in reporting this outcome one patient died and surgery was aborted and 7 patients withdrew
Selective reporting (reporting bias)	Low risk	In the protocol recorded on www.clinicaltrials.gov all outcomes reported in this review were reported.
Other bias	Low risk	

Roth 2013

Methods	Study design: Parallel group randomised controlled trial Study dates: September 2008-March 2011 Setting: University Hospital Bern, Switzerland.

Participants	Inclusion criteria: Patients undergoing radical cystectomy and ileal diversion Exclusion criteria: Previous lymph node dissection, chronic inflammatory bowel disease, radiation therapy, prior bowel surgery, severe hepatic or cardiac dysfunction, inability to consent Total number of participants randomly assigned: 157 Sex: Males, n=106, females n=51 Age: Median age of intervention group 67 (range 34-80) years; median age of control group 66 (range 30-86) years Tumour stage/ grade: Not reported Comorbidities: 14 patients had diabetes, 51 patients had an American Society of Anesthesiologists (ASA) score of III/IV Nutrition status: 34 patients were defined as malnourished based on defined criteria **Group 1: Parenteral nutrition** Number of all participants randomly assigned: 74 Age: Median 67 (range 34-80) years Sex:: Males, n=53, females, n=21 Tumour stage/ grade: Not reported Comorbidities: Diabetes 8%, ASA score III/IV 31% Nutrition status: Malnourished 15% **Group 2: Oral nutrition alone** Number of all participants randomly assigned: 83 Age: Median 66 (range 30-86) years Sex: Male, n=53, female, n=30 Tumour stage/ grade: Not reported Comorbidities: Diabetes 10%, ASA score III/IV 34% Nutrition status: Malnourished 28%
Interventions	Both groups: 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 Group 1: (n=74) Parenteral nutrition (Nutriflex special 70/240, B Braun Medical, Melsungen, Germany) All patients received 1500 ml/day for 5 days postoperatively (containing 1860 kcal, 105 g polyamino acids, 360 g glucose and 0 g lipid) Group 2: (n=83) Oral nutrition with Ringer's lactate solution (Sintetica-Bioren, Switzerland); 1500 ml/24 hours and additional potassium substitute (40 mmol)

Outcomes	Complications How measured: According to the Clavien-Dindo classification (Dindo 2004) Timepoint measured: Up to 30 days after surgery Timepoint reported: Up to 30 days Length of stay: This was reported as not differing between the two groups How measured: Number of days in hospital Timepoint measured: At discharge from hospital Timepoint reported: Number of days prior to discharge Mortality: 1 patient in each group died from complications How measured: Number of deaths Timepoint measured: Up to 30 days postoperatively Timepoint reported: Up to 30 days postoperatively
Funding sources	None
Declarations of interest	None declared
Notes	Language of publication: English The study was terminated early before enrolment targets were met following an interim statistical analysis

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomly allocated by a computer-based program" adequate sequence generation
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) Objective outcomes	Low risk	Mortality rates are not to be affected by blinding
Blinding of participants and personnel (performance bias) Subjective outcomes	Unclear risk	No blinding was reported
Blinding of outcome assessment (detection bias) Complications	Low risk	Assessed by a blinded study nurse
Blinding of outcome assessment (detection bias) Length of stay	Low risk	Length of stay is unlikely to be affected by blinding
Blinding of outcome assessment (detection bias) Mortality	Low risk	Mortality rates are not likely to be affected by blinding
Incomplete outcome data (attrition bias) Complications	Low risk	All randomised participants were included in the assessment of this outcome
Incomplete outcome data (attrition bias) Length of stay	Low risk	All randomised participants were included in the assessment of this outcome
Incomplete outcome data (attrition bias) Mortality	Low risk	All randomised participants were included in the assessment of this outcome
Selective reporting (reporting bias)	Unclear risk	No protocol was seen, outcomes described in the methods were reported.
Other bias	Low risk	No other bias was detected

Rovera 1989

Methods	Study design: Parallel group randomised controlled trial Study dates: Not reported Setting: Turin, Italy

Participants	Inclusion criteria: Patients undergoing total cystectomy for bladder cancer Exclusion criteria: Not reported Number of all participants randomly assigned: 28 Age:Not reported Sex: Male, n=22 , female, n=6 Tumour stage/ grade: Not reported Comorbidities: Not reported Nutrition status: Not reported **Group 1: Preoperative nutrition supplementation** Number of all participants randomly assigned: 12 Age: Median 66.1 (range 45-78) years Sex: Male, n=9 female, n=3 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: Male n=13, female, n=3 Tumour stage/ grade: Not reported Comorbidities: Not reported Nutrition status: Not reported
Interventions	Both groups: Post-operative parenteral nutrition (PN) commenced one day after surgery and continued for 14 days and was administered via a central line. The PN was calculated to provide 49 kcal/kg/day and 1.7 g protein per/kg/day with a nitrogen: total calorie ratio of 1:170 and with energy provided as 80% glucose and 20% fat plus vitamins, minerals and trace elements. Group 1: (n=12) Patients were provided with pre-operative oral nutritional support for 10 days prior to the surgery. The preoperative nutritional support provided to the intervention group 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 Group 2: (n=16) Patients had normal hospital diet up to the day of the operation
Outcomes	Complications How measured: Not reported Timepoint measured: Up to 30 days post surgery Timepoint reported: Up to 30 days post surgery Length of stay: Not reported Mortality: No deaths were reported How measured: Number of deaths Timepoint measured: Up to 30 days post surgery Timepoint reported: Up to 30 days post surgery
Funding sources	Not reported
Declarations of interest	Not reported

Notes	Language of publication: Italian There was no information on dietary intake in the report. Some parts of the report were not translated in sufficient detail to extract all the details.

Risk of bias table

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

Footnotes

Characteristics of excluded studies

Brodner 2001

Reason for exclusion	There was no comparison of a nutritional intervention during the randomised phase of this trial which investigated the perioperative management of patients undergoing radical cystectomy therefore this study did not meet the inclusion criteria.

Daly 1987

Reason for exclusion	Partially randomised trial examining postoperative jejunostomy feeding. The measured outcomes compare groups where randomisation did not occur therefore this trial did not meet the inclusion criteria.

de Vries 2012

Reason for exclusion	Not a RCT therefore excluded.

Hensle 1985

Reason for exclusion	In this RCT only biochemical outcomes were reported therefore did not report the outcomes specified for this review.

Karl 2014

Reason for exclusion	In this RCT nutrition supplements and the early introduction of foods post operatively 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

Reason for exclusion	This study is not a RCT therefore did not meet our inclusion criteria. It is a comparison of differing types of parenteral nutrition given to two non-randomised groups of patients post cystectomy

Mangano 1993

Reason for exclusion	This study is not a RCT therefore did nor meet our inclusion criteria.Two groups of patients who had undergone radical cystectomy were given total parenteral nutrition with or without glutamine supplementation.

McArdle 1986

Reason for exclusion	This study is not a RCT therefore did nor meet our inclusion criteria. Although this study was commenced as an RCT, after enrolment of the fourth patient, the protocol was modified to result in a cohort study with retrospective controls. The study investigated the use of elemental diet in patients undergoing radiotherapy and associated radical cystectomy

Olbert 2009

Reason for exclusion	This study 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 patients undergoing radical cystectomy

Solomon 1978

Reason for exclusion	This study did not meet our inclusion criteria. In this RCT examining 3 hypo-caloric regimens in patients undergoing urological surgery, fewer than 65% of the participants had radical cystectomy for bladder cancer (47%)

Footnotes

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

NCT03147586

Study name	Influence of Immune Nutrition Diet on 90-Day Outcomes in Patients Undergoing Radical Cystectomy
Methods	Randomised double-blinded placebo-controlled phase IV trial with two parallel treatment groups
Participants	Adults 18 years and older diagnosed with bladder cancer eligible for radical cystectomy and urinary diversions. Estimated enrolment is 100 participants
Interventions	Active Comparator: Bio-tech and omega-3 plus Bio-tech (Biopharm pharmaceutical) powder 30 mg tds. (contains multivitamins and essential amino acids) plus omega-3 plus (SEDICO pharmaceutical) capsules tds (source for omega-3 fatty acids) 1 week before and 2 week after surgery Placebo Comparator: Placebo placebo powder 30 mg tds plus placebo capsules tds for 1 week before and 2 week after surgery
Outcomes	Primary outcome: Overall 90-day postoperative complication between groups measured by modified Dindo-Clavien system Secondary outcomes 1. The effect of immune nutrition diet on nutritional status of radical cystectomy patients measured by validated nutritional assessment scores [Time Frame: 3 months]measured by validated nutritional assessment scores 2. The effect of immune nutrition diet on anthropometric measures of radical cystectomy patients measured by skinfold thickness in centimetres [Time Frame: 3 months]measured by skinfold thickness in centimetres
Starting date	March 2017
Contact information	Abdelwahab R. Hashem, Msc Mansoura, Aldakahlia, Egypt, 35516
Notes	Above details extracted from www.clinicaltrials.govThe data collection was completed in October 2017

NCT03204266

Study name	Oral Supplementation to Enhance Recovery Pilot Study
Methods	Randomized Parallel Assignment Interventional (Clinical Trial)
Participants	RC for bladder cancer with urinary diversion, 18 years and older, 46 participants
Interventions	Experimental: Immunonutrition: Arginine + Omega-3 Fatty Acids Participants take 1 ounce (30mls) of Arginine recovery supplement (ARS) four times daily 5 days preoperatively and 14 days postoperatively. Participants also given omega-3 fatty acids, 1 gram four times a day, 4 grams total per day. This will be started 7 days preoperatively and continued 14 days postoperatively.
Outcomes	Primary Outcome Determination if novel immunonutrition regimen is able to be implemented with adequate compliance in Radical Cystectomy (RC) patients: Participant Compliance [Time Frame: 21 days after starting immunonutrition regimen]Participant compliance defined as "Yes" if a participant completes at least 16 out of the total 21 days' treatment. Secondary Outcome Determination if Poor Recovery is Associated With the Use Immunonutrition Before and After Radical Cystectomy (RC): Length of Hospital Stay>7 Days [Time Frame: 90 days after surgery] Poor recovery determined by length of stay greater than 7 days. Determination if Poor Recovery is Associated With the Use Immunonutrition Before and After Radical Cystectomy (RC): Postoperative Infections [Time Frame: 90 days after surgery]Poor recovery determined by any postoperative infection. Determination if Poor Recovery is Associated With the Use Immunonutrition Before and After Radical Cystectomy (RC): Hospital Readmissions [Time Frame: 90 days after surgery]Poor recovery determined by hospital readmission within 90 days after radical cystectomy. Determination if Poor Recovery is Associated With the Use Immunonutrition Before and After Radical Cystectomy (RC): Deaths within 90 days of Cystectomy [Time Frame: 90 days after surgery]Poor recovery determined by death within 90 days of cystectomy. Decrease in Inflammatory Response of Serum Interleukin-6 Levels After Radical Cystectomy (RC) postoperative day 1 [Time Frame: 1 day after surgery]IL-6 levels drawn postoperative day 1 within 24 hours of anaesthesia induction. This used to create a response curve based on the administration of immunonutrition.
Starting date	January 17, 2018
Contact information	Neema Navai, MD Anderson Cancer CenterNational Cancer Institute (NCI)
Notes	Estimated completion August 2019 above details from clinicaltrials.gov

NCTO2238886

Study name	Radical Cystectomy, Nutrition and Convalescence: Can goal-directed postoperative nutritional therapy reduce the convalescence period for patients undergoing Radical Cystectomy (RC)? (NCT02238886)
Methods	Randomized controlled trial with Parallel Assignment
Participants	Patients aged over 18 undergoing RC who are able to give informed consent (excluded if previous radiation therapy at the pelvic area, ureterocutaneostomy or robot-assisted surgery.
Interventions	Experimental group patients receive a goal-directed nutritional intervention combining oral intake and parenteral nutrition using a dietary supplement. Parenteral nutritionI intervention: Dietary Supplement is parenteral nutrition in central vein (SMOFKABIVEN manufactured by Fresenius Kabi) The control group receive standard nutritional treatment of resting the bowel until there are signs of bowel recovery and then feeding orally.
Outcomes	The primary outcome is an assessment of quality of Life using validated questionnaires. Secondary outcomes are body-weight, hand grip strength, biochemical measures, length of hospital stay and time to bowel recovery. The follow-up period is 12 weeks.
Starting date	May 2012
Contact information	Line Noes Lydom, Rigshospitalet, Denmark
Notes	Above details extracted from www.clinicaltrials.govThe data collection was completed in December 2013, 36 participants have been recruited. The data is awaiting preparation for publication (email from contact author July 2017, no further updates received July 2018).

Footnotes

Summary of findings tables

1 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					
Outcomes	**[1] of participants (studies) Follow up**	**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 [1] [2]	RR 1.40 (1.07 to 1.82)	Study population	
				494 per 1,000	198 more per 1,000 (35 more to 405 more)
Length of stay assessed in days	157 (1 RCT)	???? LOW [1] [3]	-	The mean length of stay was 15.5 days	MD 0.5 days higher (not reported)
Mortality follow up: 30 days	157 (1 RCT)	???? VERY LOW [1] [4]	RR 1.12 (0.07 to 17.62)	Study population	
				12 per 1,000	1 more per 1,000 (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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgraded by one level due to study limitations (unclear risk of selection, performance and selective reporting bias)

[2] Downgraded by one level for serious imprecision due to wide confidence intervals that cross assumed threshold of clinical importance

[3] Downgraded by one level for suspected serious imprecision (unable to calculate confidence interval)

[4] Downgraded by two levels for very serious imprecision with very wide confidence interval

2 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, United States America.

Interventions: Immuno-enhancing nutritional supplement

Control: Standard nutritional supplement

Outcomes	**[1] of participants (studies) Follow up**	**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 [1]	RR 0.31 (0.08 to 1.23)	Study population	
				460 per 1,000	322 fewer per 1,000 (429 fewer to 107 more)
Length of stay assessed with: days	29 (1 RCT)	???? LOW[1]		The mean length of stay was 6.1 days	MD 0.2 days fewer (1.69 lower to 2.09 higher)
Mortality follow up: 30 days	29 (1 RCT)	???? LOW[1]	RR approximately 1 (no events)	Study population	
				0 per 1,000	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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgraded by two levels for very serious imprecision with very wide confidence interval

3 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	**[1] of participants (studies) Follow up**	**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 [1] [2]	RR 0.89 (0.18 to 4.51)	Study population	
				188 per 1,000	21 fewer per 1,000 (154 fewer to 658 more)
Length of stay - not measured	-	-	-	-	-
Mortality follow up: 30 days	28 (1 RCT)	???? VERY LOW [1] [2]	RR approximately 1 (no events)	Study population	
				0 per 1,000	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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgraded by one level due to study limitations (unclear risk of selection, performance, attrition and selective reporting bias)

[2] Downgraded by two levels for very serious imprecision with very wide confidence interval

4 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: Hospital, United States of America

Interventions: Early enteral feeding after surgery

Control: Standard care

Outcomes	[1] of participants (studies) Follow up	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 [1] [2]	RR 1.14 (0.85 to 1.53)	Study population	
				596 per 1,000	83 more per 1,000 (89 fewer to 316 more)
Length of stay assessed with: days	102 (1 RCT)	???? LOW [1] [3]	-	The mean length of stay was 9.7 days	MD 0.95 days fewer (unable to calculate CI)
Mortality follow up: 30 days	102 (1 RCT)	???? LOW[1] [3]	RR 0.52 (0.10 to 2.71)	Study population	
				38 per 1,000	19 fewer per 1,000 (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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgraded by one level for study limitations (unclear risk of selection and performance bias)

[2] Downgraded by two levels for very serious imprecision with very wide confidence interval

[3] Downgraded one level for serious imprecision (unable to calculate confidence interval)

5 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, United States of America

Interventions: Amino acid solutions

Control: Dextrose

Outcomes	[1] of participants (studies) Follow up	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 [1 2 3]	RR 0.77 (0.32 to 1.82)	Study population	
				200 per 1,000	46 fewer per 1,000 (136 fewer to 164 more)
Length of stay in days	44 (1 RCTs)	???? VERY LOW [1 2 3]	-	The mean length of stay was 32 days	MD 0.5 days fewer
Mortality follow up: 30 days	60 (1 RCT)	???? VERY LOW [1 2 3]	RR approximately 1 (no events)	Study population	
				0 per 1,000	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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgraded by one level due to study limitations (unclear and high risk of selection bias; unclear risk of performance, detection and selective reporting bias)

[2] Downgraded for by one level due to serious indirectness related to patient population

[3] Downgraded by two levels due to very serious imprecision with very wide confidence intervals

6 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, United States of America

Interventions: Branch chain amino acids

Control: Dextrose

Outcomes	[1] of participants (studies) Follow up	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 [1 2 3]	RR approximately 1 (no events)	Study population	
				0 per 1,000	Unable to calculate
Length of 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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgraded by one level due to study limitations.

[2] Downgraded for by one level due to serious indirectness related to patient population

[3] Downgraded by two levels due to very serious imprecision with very wide confidence intervals

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, United States of America
Intervention: oral nutritional supplements
Comparison: multivitamin and mineral supplement

Outcomes	[1] of participants (studies) Follow up	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 [1] [2]	RR 0.73 (0.47 to 1.13)	Study population	
				500 per 1,000	135 fewer per 1,000 (265 fewer to 65 more)
Length of stay	61 (1 RCT)	???? LOW [1] [2]	-	The mean length of stay was 8.9 days	MD 0.3 days lower (3.64 lower to 3.04 higher)
Mortality follow up: 30 days	61 (1 RCT)	???? LOW [1] [2]	RR 0.97 (0.06 to 14.78)	Study population	
				33 per 1,000	1 fewer per 1,000 (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; **RR:** Risk ratio; **OR:** Odds 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

Footnotes

[1] Downgrade one level for study limitations (unclear selection, performance and detection bias)

[2] Downgrade one level due to imprecision and wide confidence intervals

Additional tables

1 Description of interventions

	Intervention(s) [route, frequency, total dose/day]	Intervention(s) appropriate as applied in a clinical practice setting[a] [description]	Comparator(s) [route, frequency, total dose/day]	Comparator(s) appropriate as applied in a clinical practice setting[a] [description]
Hamilton-Reeves 2016	**I1**: immuno-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 1500mls/day (1860Kcals, 150g AA, 360g glucose)	Postoperatively	C1: Oral nutrition with Ringer's lactate solution with additional potassium 1500mls/24 hours	For 5 days postoperatively
Rovera 1989	**I1**: oral nutritional supplements (Precision N, 30 kcal/kg/day,1.5g 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 Kcals/kg/day,1.5g of protein/Kg/day) **I2**: AA solution with 45% branch chain AA (30 Kcals/kg/day, 1.5g of protein/Kg/day)	Started postoperative day 1 and stopped postoperative day 8	C1: dextrose 150g in 3 litres 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 (1.3-1.5g/kg/day) **I2**: intravenous fluids containing dextrose and AA (1.3-1.5g/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 0.7-1.0g/kg/day and calories 240kcals/day	Postoperative Duration -	C1: 5% dextrose	Postoperative Duration -

- denotes not reported

[a]The 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; **g:** grams; **I**: Intervention; **Kg**: Kilogrames; **N/CPS**: no specification of clinical practice setting possible

Footnotes

2 Baseline characteristics

	Intervention(s) and comparator(s)	Duration of intervention (duration of follow-up) [days, months. years, etc.]	Trial period [year to year]	Country	Setting	Ethnic groups [%]
Hamilton-Reeves 2016	**I1**: immuno-nutrition supplement	5 days pre and 5 days postoperatively. (Followed up for 90 days postoperatively)	2013-2015	USA	Home and hospital	-
	C1: oral nutrition supplement					-
Ritch 2018	**I1**: oral nutritional supplements	(Followed up for 30 days postoperatively)	April 2014-December 2016	USA	Home and hospital	
	C1: multivitamin and mineral supplements					
Deibert 2016	**C1**: normal diet	Duration - (Followed 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 (Followed up for 30 days postoperatively)	2008-2011	Switerland	Hospital	-
	C1: oral nutrition with Ringer's lactate solution					-
Rovera 1989	**I1**: oral nutritional supplements	10 days preoperatively (Followed up for 30 days postoperatively)	-	Italy	-	-
	C1: normal diet					-
Bonau 1984	**I1**: AA solution with 25% branch chain AA	Frome postoperative days 1 - 8 (Follow up -)	-	USA	Hospital	
	I2: AA solution with 45% branch chain AA					-
	C1: dextrose					-
Hensle 1978	**I1**: intravenous fluids containing dextrose and AA	Duration - (Follow up 60 days)	-	USA	Hospital	-
	C1: 5% dextrose					-

Footnotes

- denotes not reported

AA: amino acid; **C**: Comparator; **I**: Intervention

References to studies

Included studies

Bonau 1984

Bonau RA, Ang SD, Jeevanandam M, Daly JM. High-branched chain amino acid solutions: relationship of composition to efficacy. Journal of Parenteral and Enteral Nutrition 1984;8(6):622-7.

Daly 1982

Daly J, Copeland E, Johnson D, Massar E, Dudrick S. Effects of perioperative infusion of dextrose and amino acid solutions in bladder cancer patients. Clinical Nutrition 1982;1:98.

Deibert 2016

Deibert CM, Silva MV, RoyChowdry A, McKiernan J, Scherr DS, Seres D, et al. A prospective randomized trial of the effects of early enteral feeding after radical cystectomy. Urology 2016;96:69-73.

Hamilton-Reeves 2016

Hamilton-Reeves JM, Bechtel MD, Hand LK, Schleper A, Yankee TM, Eugene PC, et al. Effects of Immunonutrition for

Cystectomy on Immune Response and Infection Rates: A Pilot Randomized Controlled Clinical Trial. European Urology 2016;69:389-92.

Hensle 1978

* Hensle, TW. Protein-sparing in cystectomy patients. Journal of Parenteral and Enteral Nutrition 1978;2(4):519-23.

Ritch, 2018

Ritch, C. R., Cookson, M. S., Clark, P. E., et al. Perioperative Oral Nutrition Supplementation Reduces Prevalence of Sarcopenia following Radical Cystectomy: Results of a Prospective Randomized Controlled Trial. Journal of Urology 2018.

Roth 2013

Faune AV, Kiss B, Burkhard FC, Studer LE, Thalmann GN, Roth B. Administration of postoperative parenteral nutrition does not affect oncological outcomes after radical cystectomy (RC) in bladder cancer patients. In: Journal of Urology: Conference Abstract Annual Meeting of the American Urological Association 2015. Vol. 193 (4 SUPPL 1) e813. 2015.

* Roth B, Birkhauser FD, Zehnder P, Thalmann GN, Huwyler M, Burkhard FC, et al. Parenteral nutrition does not improve postoperative recovery from radical cystectomy: results of a prospective randomised trial. European Urology 2013; 63(3):475-82.

Vidal Faune A, Arnold N, Vartolomei M, Kiss B, Burkhard FC, Thalmann GN, et al. Does postoperative parenteral nutrition after radical cystectomy impact oncological and functional outcomes in bladder cancer patients? In: European Urology, Supplements. Conference:31st Annual Congress of the European Association of Urology, EAU16. Vol. 15 (3)pp e515. 2016.

Rovera 1989

* Rovera L, Rolle G, Alliaudi C, Aloi MR, Buffa G, Cocimano V, et al. (Usefulness of preoperative nutritional support in patients with bladder carcinoma) [Utilità di un supporto nutrizionale preoperatorio in pazienti affetti da carcinoa vescicale]. Rivista italiana di Nutrizione ed Enterale 1989;7(2):79-85.

Excluded studies

Brodner 2001

Brodner G, Van Aken H, Hertle L, Fobker M, Von Eckardstein A, Goeters C, et al. Multimodal perioperative management--combining thoracic epidural analgesia, forced mobilization, and oral nutrition-reduces hormonal and metabolic stress and improves convalescence after major urologic surgery. Anesthesia and Analgesia 2001;92(6):1594-600. [PubMed: 11375853]

Daly 1987

Daly JM, Bonau R, Stofberg P, Bloch A, Jeevanandam M, Morse M. Immediate postoperative jejunostomy feeding clinical and metabolic results in a prospective trial. American Journal of Surgery 1987;153(2):198-206. [PubMed: 3101530]

de Vries 2012

de Vries RR, Kauer P, van Tinteren H, van der Poel HG, Bex A, Meinhardt W, et al. Short-term outcome after cystectomy: comparison of two different perioperative protocols. Urologia Internationalis 2012;88(4):383-9. [PubMed: 22433508]

Hensle 1985

Hensle TW, Askanazi J, Rosenbaum LH, Bernstein G, Kinney JM. Metabolic Changes Associated with Radical Cystectomy. The Journal of Urology 1985;Nov; 134 (5):1032-6.

Karl 2014

Karl A, Buchner A, Becker A, Staehler M, Seitz M, Khoder W, et al. A new concept for early recovery after surgery for patients undergoing radical cystectomy for bladder cancer: results of a prospective randomized study. Journal of Urology 2014;191:335-40.

Malossini 1987

Malossini G, Cavalleri S, Bianchi G, Carpi I, Lamberti L, Scroccaro G. [Protein-sparing peripheral parenteral nutrition in urologic surgery] [Nutrizione parenterale periferica "protein sparing" nella chirurgia urologica.]. Chirurgia italiana 1987; 39(5):489-95. [PubMed: 3121199]

Mangano 1993

Mangano A, Panza N, Paganini N, Croce G, Cassone E, Trevisan M, et al. (Effects of parenteral glutamine supplementation on the nutritional status of patients with radical cystectomy in neoplasia) [Effetti della supplementazione parenterale di glutammina sullo stato nutrizionale di pazienti sottoposti a cistectomia radicale per neoplasia]. Acta Urologica Italica 1993;7 (Suppl 2):119-20.

McArdle 1986

McArdle AH, Reid EC, Laplante MP, Freeman CR. Prophylaxis against radiation injury. The use of elemental diet prior to and during radiotherapy for invasive bladder cancer and in early postoperative feeding following radical cystectomy and ileal conduit. Archives of Surgery 1986;121(8):879-85. [PubMed: 3089195]

Olbert 2009

Olbert PJ, Baumann L, Hegele A, Schrader AJ, Hofmann R. [Fast-track concepts in the perioperative management of patients undergoing radical cystectomy and urinary diversion: review of the literature and research results] [Fast-track-Konzepte im perioperativen Management bei Zystektomie und Harnableitung: Literaturubersicht und eigene Ergebnisse]. Der Urologe. Ausg. A 2009;48(2):137-42. [PubMed: 19142627]

Solomon 1978

Solomon MJ, Smith MF, Dowd JB, Bistrian BR, Blackburn GL. Optimal nutritional support in surgery for bladder cancer: preservation of visceral protein by amino acid infusions. The Journal of Urology 1978;119(3):350-4. [PubMed: 565418]

Studies awaiting classification

Ongoing studies

NCT03147586

* Influence of Immune Nutrition Diet on 90-Day Outcomes in Patients Undergoing Radical Cystectomy. clinicaltrials.gov/ct2/show/ accessed 12 July 2018.

NCT03204266

Oral Supplementation to Enhance Recovery Pilot Study. https://clinicaltrials.gov/ct2/show/NCT03204266 accessed 12 July 2018.

NCTO2238886

Radical Cystectomy, Nutrition and Convalescence: Can goal-directed postoperative nutritional therapy reduce the convalescence period for patients undergoing Radical Cystectomy (RC)? https://clinicaltrials.gov/ct2/show/NCT02238886 accessed July 2014.

Other references

Additional references

Arumainayagam 2008

Arumainayagam N, McGrath J, Jefferson KP, Gillatt DA. Introduction of an enhanced recovery protocol for radical cystectomy. BJU International 2008;101(6):698-701. [PubMed: 18190646]

Askanazi 1986

Askanazi J, Hensle TW, Starker PM, Lockhart SH, LaSala PA, Olsson C, et al. Effect of immediate postoperative nutritional support on length of hospitalization. Annals of Surgery 1986;203(3):236-9. [PubMed: 3082301]

Azhar 2016

Azhar, R. A., Bochner, B., Catto, J., Goh, A. C.Kelly, J.Patel, H. D.Pruthi, R. S.Thalmann, G. N.Desai, M. Enhanced Recovery after Urological Surgery: A Contemporary Systematic Review of Outcomes, Key Elements, and Research Needs. European Urology 2016;70(1):176-187. [DOI: 10.1016/j.eururo.2016.02.051]

Barrass 2006

Barrass BJ, Thurairaja R, Collins JW, Gillatt D, Persad RA. Optimal nutrition should improve the outcome and costs of radical cystectomy. Urologia Internationalis 2006;77:139-42.

Billson 2013

Billson HA, Holland C, Curwell J, Davey VL, Kinsey L, Lawton LJ, et al. Perioperative nutrition interventions for women with ovarian cancer. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD009884 DOI: 10.1002/14651858.CD009884.

Braud 2002

de Braud F, Maffezzini M, Vitale V, Bruzzi P, Gatta G, Hendry WF, et al. Bladder cancer. Critical Reviews in Oncology/hematology 2002;41:89-106.

Burden 2012a

Burden S, Todd C, Hill J, Lal S. Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD008879 DOI: 10.1002/14651858.CD008879.pub2.

Burden 2017

Burden ST, Gibson D, Lal S, Hill J, Pilling M, Soop M, Aswarth R, Todd C. Pre-operative oral nutritional supplementation with dietary advice versus dietary advice alone in weight-losing patients with colorectal cancer: single-blind randomized controlled trial. Journal of Cachexia, Sarcopenia and Muscle 2017;8(3):437-446. [DOI: 10.1002/jcsm.12170]

Cerantola 2013

Cerantola Y, Valerio M, Persson B, Jichlinski P, Ljungqvist O, Hubner M, et al. Guidelines for perioperative care after radical cystectomy for bladder cancer: Enhanced Recovery After Surgery (ERAS®) Society recommendations. Clinical Nutrition 2013;32:879-87.

Chin 1983

Chin JL, Wyatt JK. Effects of total parenteral nutrition on patients with bladder cancer who undergo cystectomy. The Canadian Journal of Surgery 1983;26(6):495-8.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger M, Davey Smith G, Altman DG, editors(s). Systematic Reviews in Health Care: Meta-Analysis in Context. 2nd edition. London: BMJ Publication Group, 2001.

Dindo 2004

Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. Annals of Surgery 2004;2:205-13.

Giulia 2017

Giulia Villa, Martina Bresciani, Mattia Boarin, F Manara Duilio. The impact of oral nutrition in patients after radical cystectomy: an overview. International Journal of Urological Nursing 2017;11(3):136-43.

GLOBOCAN 2012

Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 v.1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France: International Agency for Research on Cancer; 2013. Available from http://globocan.iarc.fr (accessed 3 September 2014).

GRADEpro GDT

GRADEpro GDT [Computer program]. Version accessed 2 June 2017. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.Available at gradepro.org.

Gregg 2011

Gregg JR, Cookson MS, Phillips S, Salem S, Chang SS, Clark PE, et al. Effect of preoperative nutritional deficiency on mortality after radical cystectomy for bladder cancer. The Journal of Urology 2011;185(1):90-6. [PubMed: 21074802]

Guyatt 2008

Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Schünemann HJ, et al. GRADE: what is "quality of evidence" and why is it important to clinicians? BMJ (Clinical Research Ed.) 2008;336(7651):995-8. [DOI: 10.1136/bmj.39490.551019.BE]

Henry 2011

Henry C. Chapter 4, Effect of malnutrition on cancer patients. In: Shaw C, editors(s). Nutrition and Cancer. Wiley-Blackwell, 2011:46.

Heyland 2001

Heyland DK, Montalvo M, MacDonald S, Keefe L, Su XY, Drover JW. Total parenteral nutrition in the surgical patient: a meta-analysis. Canadian Journal of Surgery 2001;44(2):102-11. [PubMed: 11308231]

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557-60.

Higgins 2011

Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

Hollenbeck 2006

Hollenbeck BK, Miller DC, Taub DA, Dunn RL, Khuri SF, Henderson WG, et al. The effects of adjusting for case mix on mortality and length of stay following radical cystectomy. The Journal of Urology 2006;176(4 Pt 1):1363-8. [PubMed: 16952633]

Jensen 2018

Jensen Bente T, Lauridsen Susanne V, Jensen Jørgen B. Prehabilitation for major abdominal urologic oncology surgery. Current Opinion in Urology 2018;28(3):243-50.

Karl 2009

Karl A, Rittler P, Buchner A, Fradet V, Speer R, Walther S, et al. Prospective assessment of malnutrition in urologic patients. Urology 2009;73(5):1072-6.

Kondrup 2003

Kondrup J, Allison SP, Elia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. Clinical Nutrition 2003; 22(4):415-21. [PubMed: 12880610]

Lawrie 2018

Lawrie Theresa A., Green, John T., Beresford, Mark, et al. Interventions to reduce acute and late adverse gastrointestinal effects of pelvic radiotherapy for primary pelvic cancers. Cochrane Database of Systematic Reviews 2018, Issue No.: CD012529. Art. No.: CD012529 DOI: 10.1002/14651858.CD012529.pub2.

Maffezzini 2006

Maffezzini M, Gerbi G, Campodonico F, Parodi D. A multimodal perioperative plan for radical cystectomy and urinary intestinal diversion: effects, limits and complications of early artificial nutrition. The Journal of Urology 2006;176(3):945-8; discussion 948-9. [PubMed: 16890663]

Maffezzini 2008

Maffezzini M, Campodonico F, Canepa G, Gerbi G, Parodi D. Current perioperative management of radical cystectomy with intestinal urinary reconstruction for muscle-invasive bladder cancer and reduction of the incidence of postoperative ileus. Surgical Oncology 2008;17(1):41-8.

Mathur 2007

Mathur S, Plank LD, Hill AG, Rice MA, Hill GL. Changes in body composition, muscle function and energy expenditure after radical cystectomy. BJU International 2007;101:973-7.

Matulewicz 2015

Matulewicz RS, Brennan J, Pruthi RS, Kundu SD, Gonzalez CM, Meeks JJ.. Radical Cystectomy Perioperative Care Redesign.. Urology Dec 2015;86((6)):1076-86.

Melnyk 2011

Melnyk M, Casey RG, Black P, Koupparis AJ. Enhanced recovery after surgery (ERAS) protocols: time to change practice? Canadian Urological Association Journal 2011;5(5):342-8.

Mohler 1987

Mohler JL, Flanigan RC. The effect of nutritional status and support on morbidity and mortality of bladder cancer patients treated by radical cystectomy. The Jounal of Urology 1987;137:404-8.

Mueller 2011

Mueller C, Compher C, Ellen DM; American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.) Board of Directors. A.S.P.E.N. clinical guidelines: Nutrition screening, assessment, and intervention in adults. Journal of Parenteral and Enteral Nutrition 2011;35(1):16-24. [PubMed: 21224430]

Munbauhal 2014

Munbauhal G, Drouin SJ, Mozer P, Colin P, Phé V, Cussenot O, et al. Malnourishment in bladder cancer and the role of immunonutrition at the time of cystectomy: an overview for urologists. BJU International 2014;114(2):177-84.

NICE 2006

CG32 Nutrition support in adults: oral nutrition support, enteral tube feeding and parenteral nutrition. National Institute for Health and Care Excellence; 2006 Feb. NICE clinical guideline 32. Available from guidance.nice.org.uk/cg32.

NICE 2015

National Institute for Health and Care Excellence. NG2 Bladder cancer: diagnosis and management. nice.org.uk/guidance/ng2 2015.

Pruthi 2003

Pruthi RS, Chun J, Richman M. Reducing time to oral diet and hospital discharge in patients undergoing radical cystectomy using a perioperative care plan. Urology 2003;62(4):661-5; discussion 665-6. [PubMed: 14550438]

Rattray 2018

M Rattray, S Roberts, A Marshall, B Desbrow. A systematic review of feeding practices among postoperative patients: is practice in-line with evidenced-based guidelines? Journal of Human Nutrition and Dietetics 2018;31(2):151-67. [DOI: 10.1111/jhn.12486]

Review Manager 2014

Review Manager 5 (RevMan 5) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schünemann 2011

Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Shabsigh 2009

Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, et al. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. European Urology 2009;55:164-76.

Smith 2014

Smith AB, Deal AM, Yu H, Boyd B, Matthews J, Wallen EM, et al. Sarcopenia as a predictor of complications and survival following radical cystectomy. Journal of Urology 2014;191(6):1714-20.

South West Public Health Observatory 2011

South West Public Health Observatory (SWPHO), UK. Survival in patients treated by cystectomy for bladder cancer, Urological Cancers SSCRG. National Cancer Intelligence Network 2011.

Stein 2003

Stein JP, Skinner DG. Results with radical cystectomy for treating bladder cancer: a 'reference standard' for high-grade, invasive bladder cancer. BJU International 2003;92:12-7.

Sterne 2011

Sterne JAC, Egger M, Moher D (editors). Chapter 10: Addressing reporting biases. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Thurairaja 2005

Thurairaja R, Whittleston T, McFarlane J, Persad R. Is nutritional support beneficial to patients after cystectomy? BJU International 2005;95(9):1168-70. [PubMed: 15892795]

Tobias 2010

Tobias J, Hochhauser D. Cancer and its Management. 6th edition. Wiley-Blackwell, 2010.

Weimann 2017

Weimann Arved, Braga Marco, Carli Franco, Higashiguchi Takashi, Hübner Martin, Klek Stanislaw, et al. ESPEN guideline: Clinical nutrition in surgery. Clinical Nutrition 2017;36(3):623-50.

Other published versions of this review

Burden 2012b

Burden S, Billson HA, Lal S, Sharma A, Lyell C, Owen KA, et al. Perioperative nutrition for the treatment of bladder cancer by radical cystectomy. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD010127 DOI: 10.1002/14651858.CD010127.

Classification pending references

Data and analyses

1 Postoperative parenteral nutrition compared to standard care

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Complications	1	157	Risk Ratio(M-H, Random, 95% CI)	1.40 [1.07, 1.82]
1.2 Mortality	1	157	Risk Ratio(M-H, Random, 95% CI)	1.12 [0.07, 17.62]

2 Immunonutrition compared to standard oral nutritional supplements

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Complications 90 days	1	29	Risk Ratio(M-H, Random, 95% CI)	0.31 [0.08, 1.23]
2.2 Complications 30 days	1	29	Risk Ratio(M-H, Random, 95% CI)	0.97 [0.62, 1.53]
2.3 Length of stay	1	29	Mean Difference(IV, Random, 95% CI)	0.20 [-1.69, 2.09]

3 Preoperative oral nutritional support compared to normal diet

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
3.1 Complications	1	28	Risk Ratio(M-H, Random, 95% CI)	0.89 [0.18, 4.51]

4 Early postoperative feeding compared to standard postoperative management

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
4.1 Complications	1	102	Risk Ratio(M-H, Random, 95% CI)	1.14 [0.85, 1.53]
4.2 mortality	1	102	Risk Ratio(M-H, Random, 95% CI)	0.52 [0.10, 2.71]

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

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
5.1 Complications	2	104	Risk Ratio(M-H, Random, 95% CI)	0.77 [0.32, 1.82]

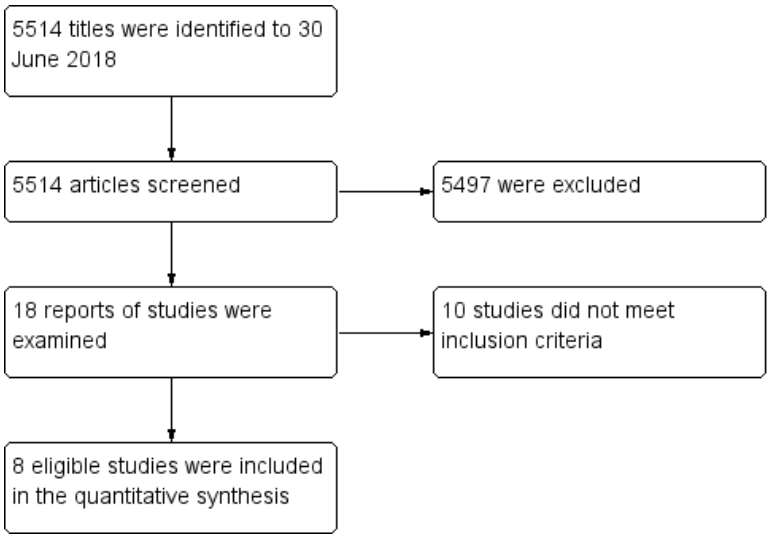
5.2 Length of stay	2	104	Mean Difference(IV, Random, 95% CI)	Not estimable
5.3 Mortality	1	60	Risk Ratio(M-H, Random, 95% CI)	Not estimable

7 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
7.1 Complications	1	61	Risk Ratio(M-H, Random, 95% CI)	0.73 [0.47, 1.13]
7.2 Length of stay	1	61	Mean Difference(IV, Random, 95% CI)	-0.30 [-3.64, 3.04]
7.3 mortality	1	61	Risk Ratio(M-H, Random, 95% CI)	0.97 [0.06, 14.78]

Figures

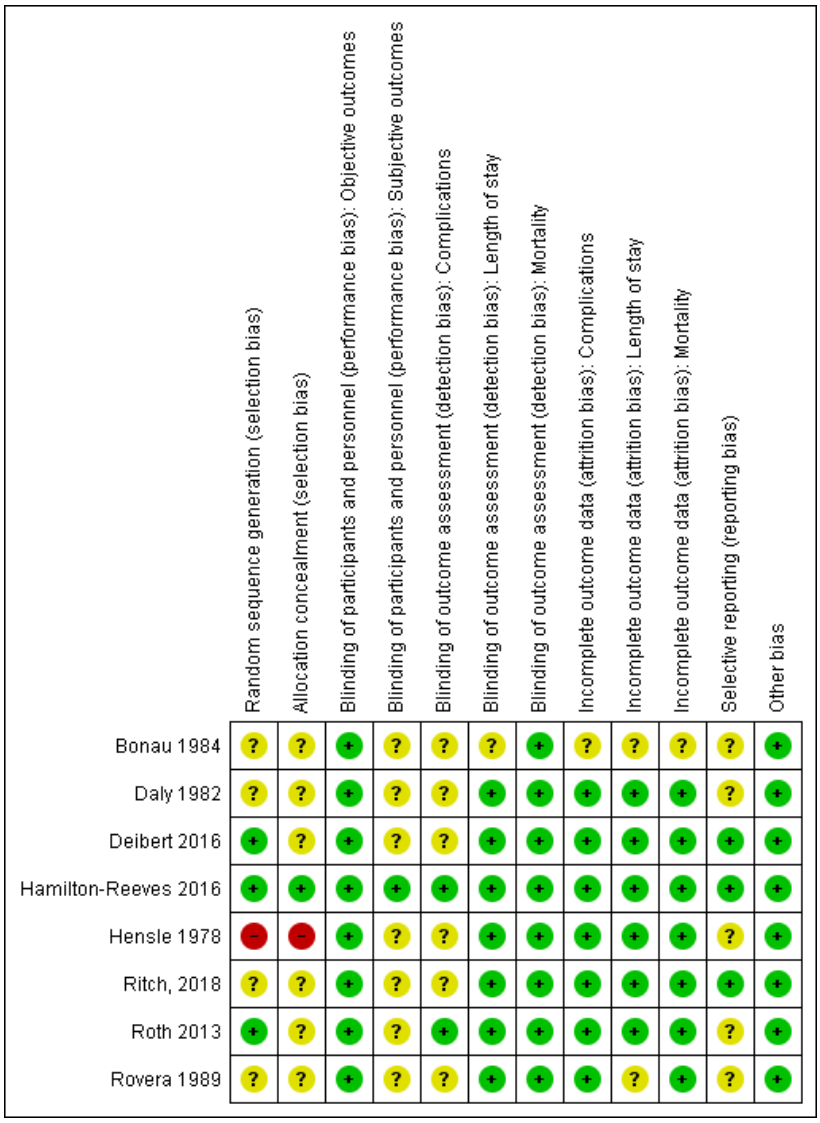
Figure 1



Caption

Study flow diagram.

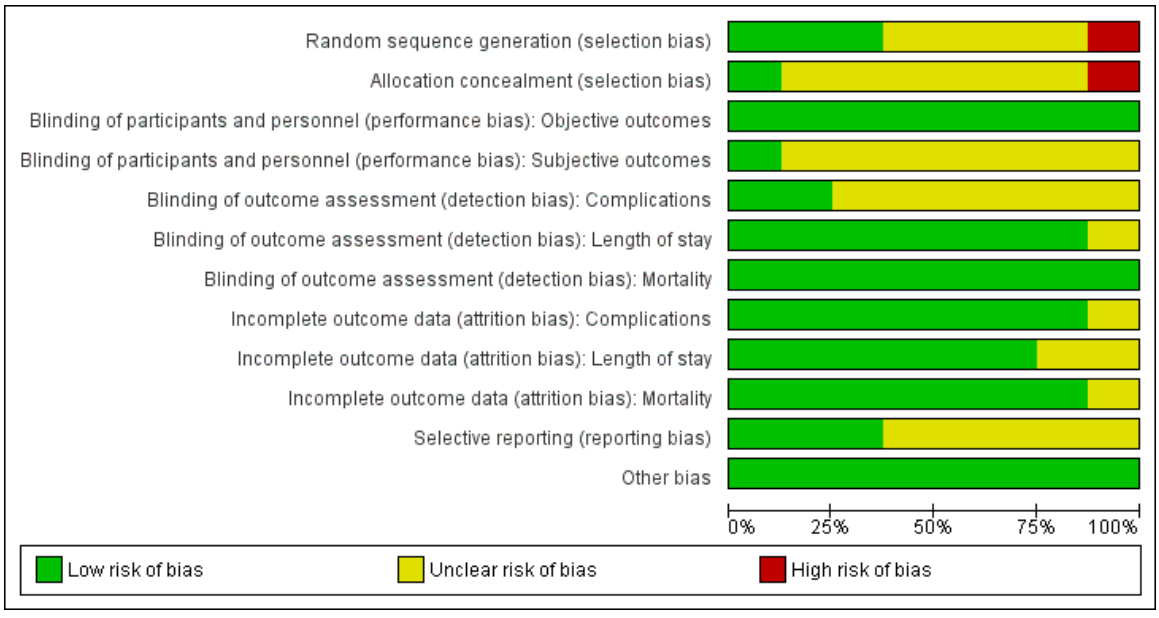
Figure 2



Caption

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

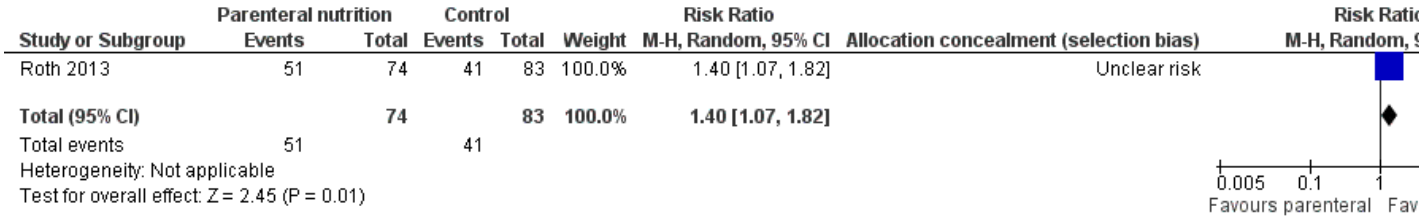
Figure 3



Caption

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

Figure 4 (Analysis 1.1)

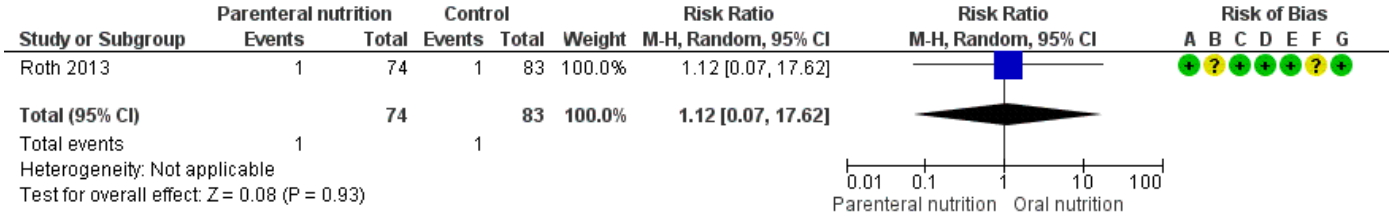


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Subjective outcomes
(D) Blinding of outcome assessment (detection bias): Complications
(E) Incomplete outcome data (attrition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

Caption

Forest plot of comparison 1: Postoperative parenteral nutrition vs standard care, outcome: 1.1 Complications.

Figure 5 (Analysis 1.2)

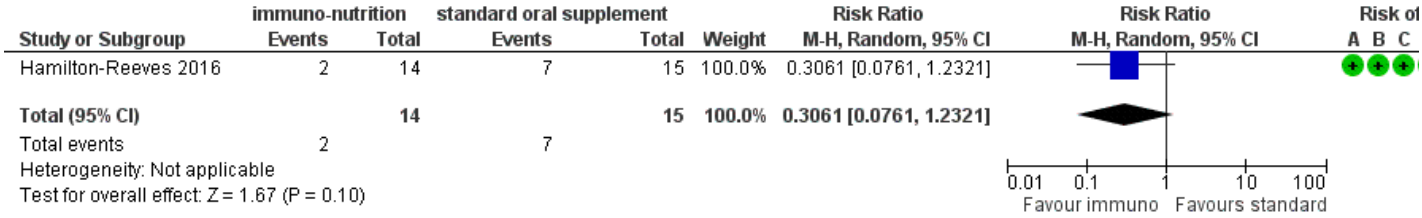


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Objective outcomes
(D) Blinding of outcome assessment (detection bias): Mortality
(E) Incomplete outcome data (attrition bias):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

Caption

Forest plot of comparison: 1 Postoperative parenteral nutrition compared to standard care, outcome: 1.2 Mortality.

Figure 6 (Analysis 2.1)

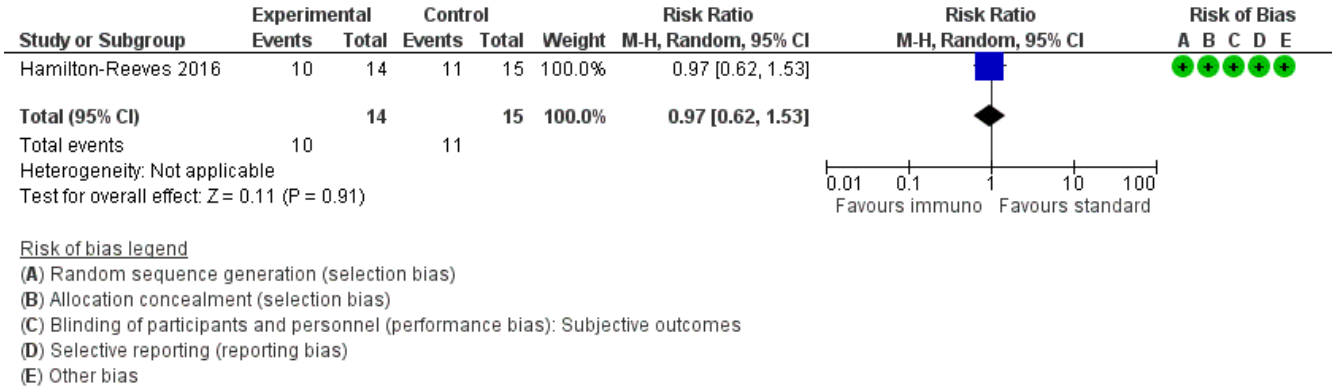


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias): Subjective outcomes
(D) Selective reporting (reporting bias)
(E) Other bias

Caption

Forest plot of comparison: 2 Immunonutrtion compared to standard oral nutritional supplements, outcome: 2.2 Complications 90 days.

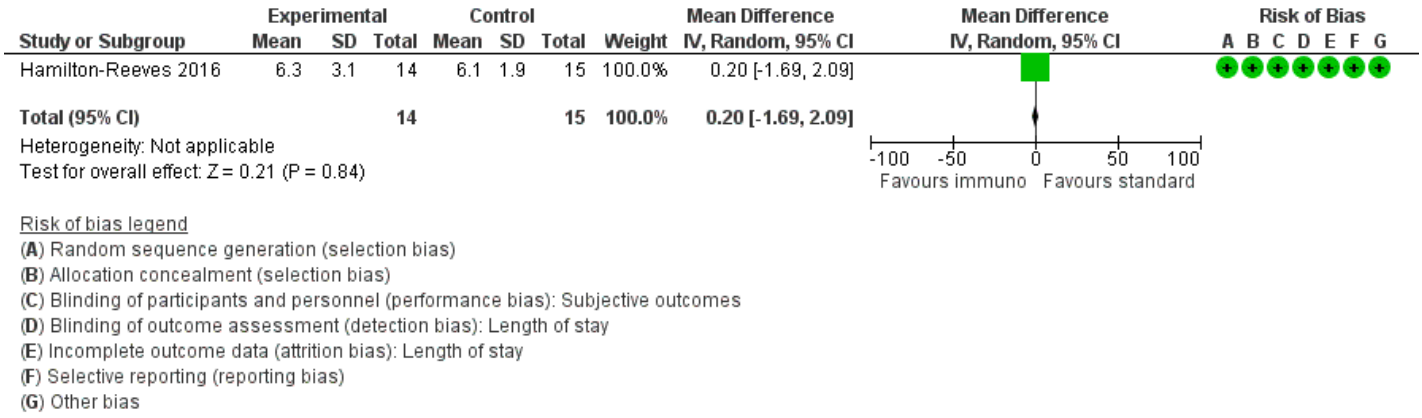
Figure 7 (Analysis 2.2)



Caption

Forest plot of comparison: 2 Immunonutrtion compared to standard oral nutritional supplements, outcome: 2.1 Complications 30 days.

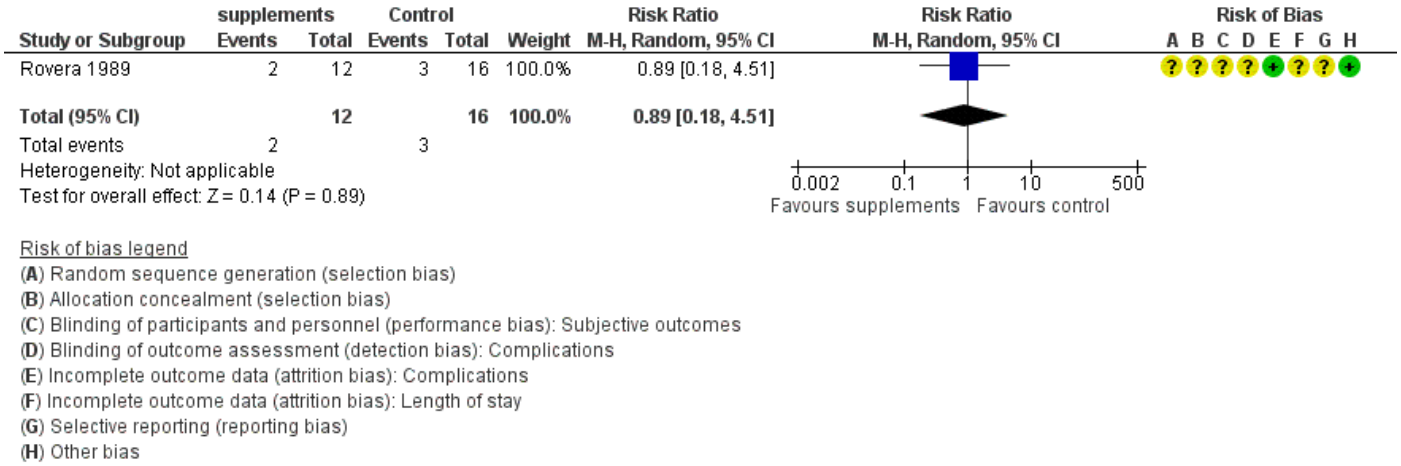
Figure 8 (Analysis 2.3)



Caption

Forest plot of comparison: 2 Immunonutrtion compared to standard oral nutritional supplements, outcome: 2.3 Length of stay.

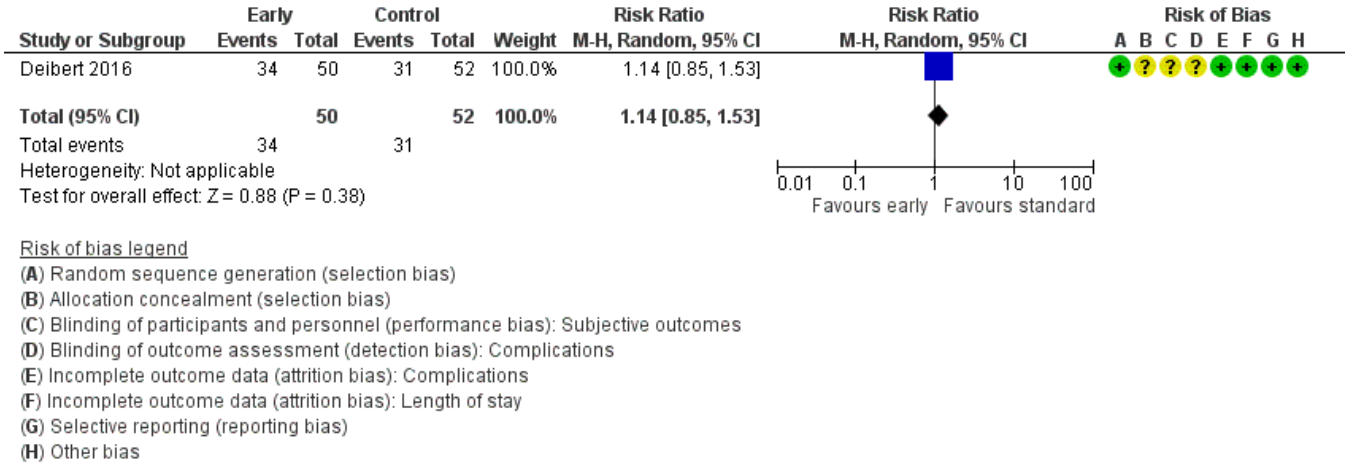
Figure 9 (Analysis 3.1)



Caption

Forest plot of comparison: 3 Preoperative oral nutritional support compared to normal diet, outcome: 3.1 Complications.

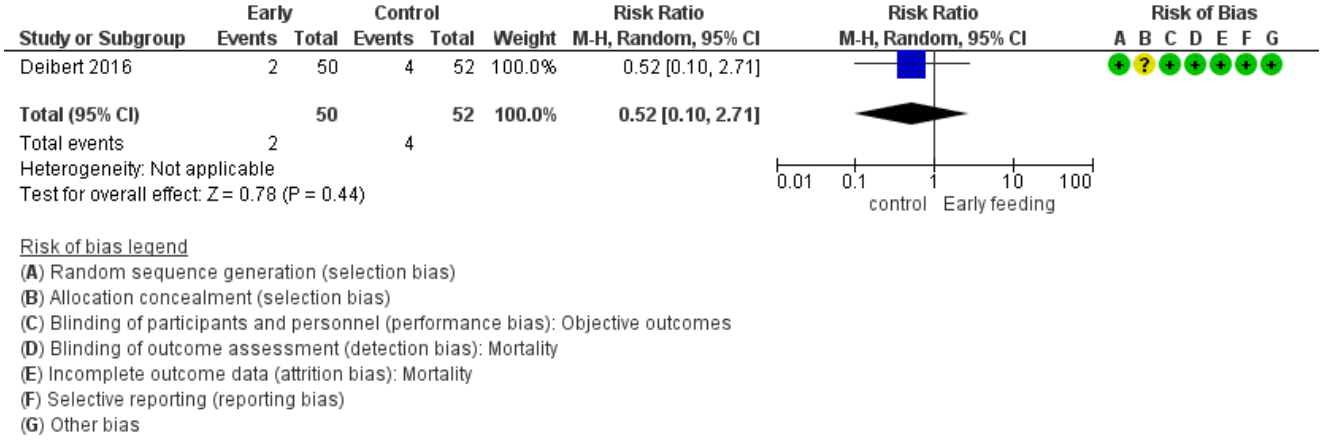
Figure 10 (Analysis 4.1)



Caption

Forest plot of comparison: 4 Early postoperative feeding compared to standard postoperative management, outcome: 4.1 Complications.

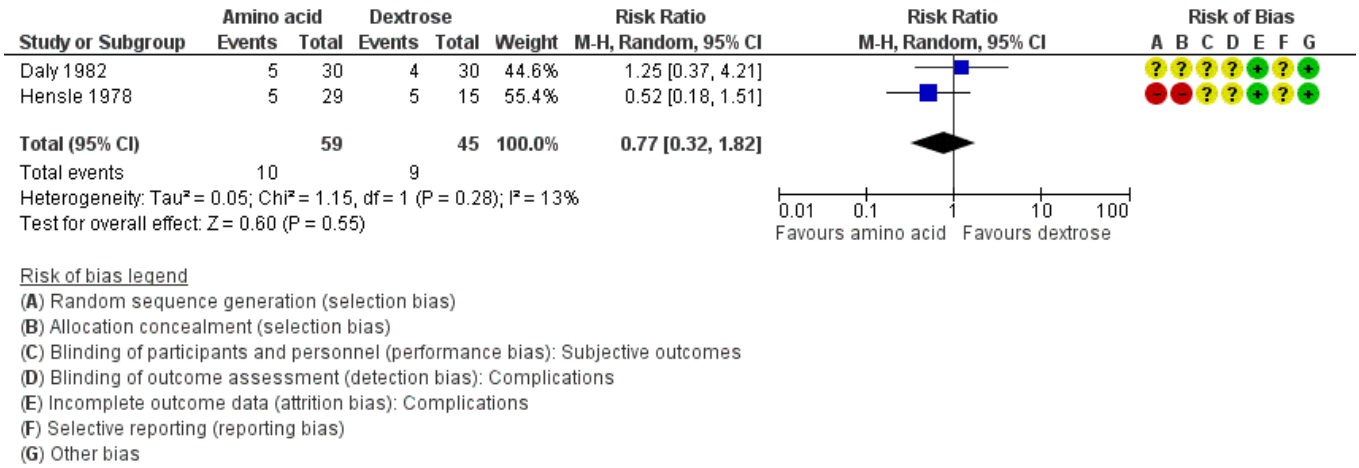
Figure 11 (Analysis 4.2)



Caption

Forest plot of comparison: 4 Early postoperative feeding compared to standard postoperative management, outcome: 4.2 mortality.

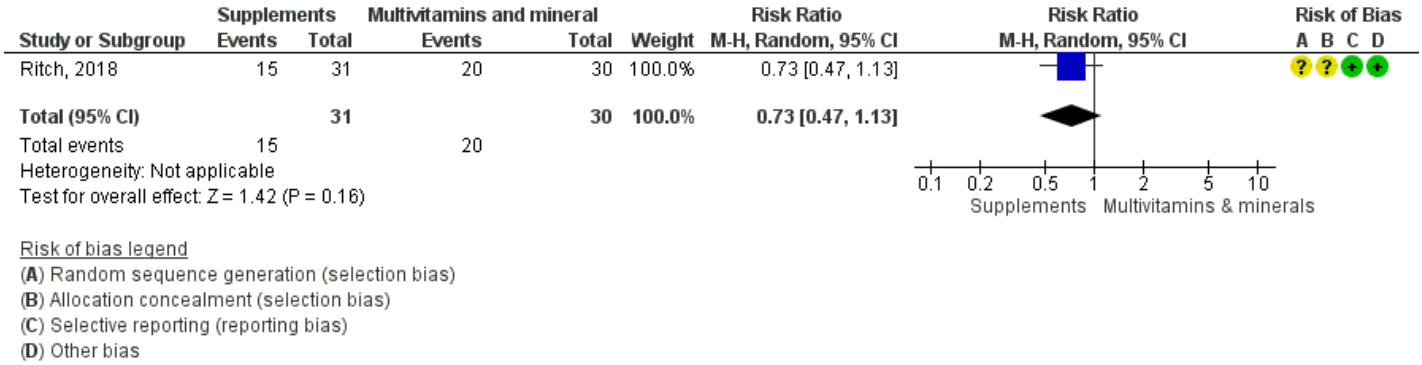
Figure 12 (Analysis 5.1)



Caption

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

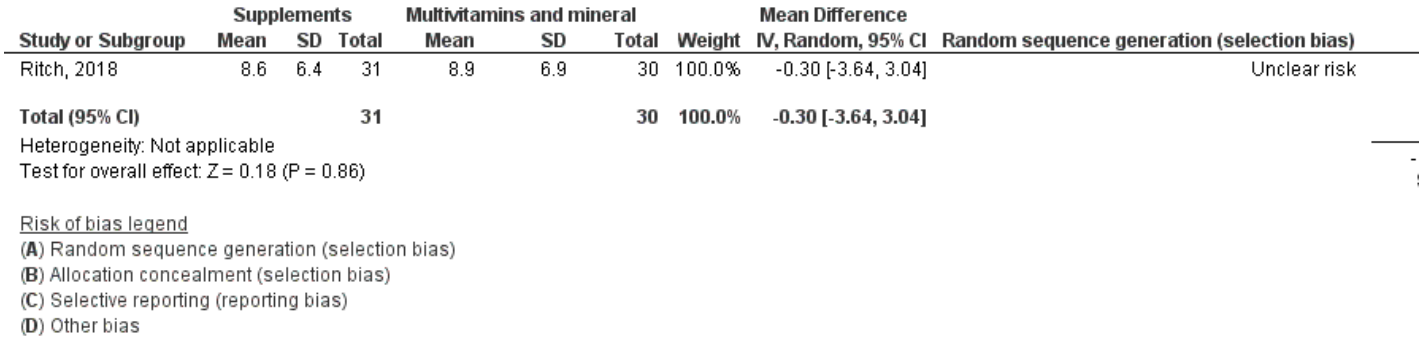
Figure 13 (Analysis 7.1)



Caption

Forest plot of comparison: 7 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement, outcome: 7.1 Complications.

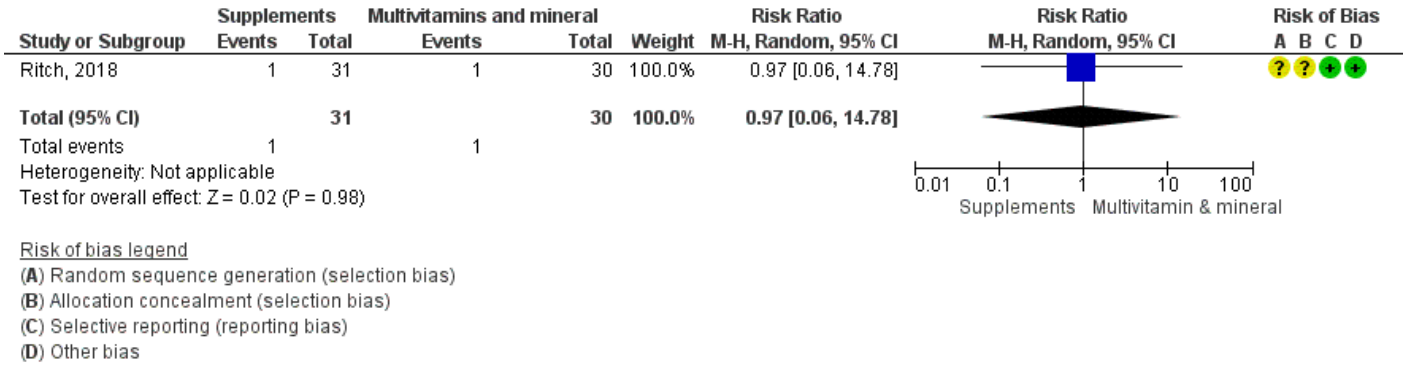
Figure 14 (Analysis 7.2)



Caption

Forest plot of comparison: 7 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement, outcome: 7.2 Length of stay.

Figure 15 (Analysis 7.3)



Caption

Forest plot of comparison: 7 Perioperative oral nutritional supplements compared to oral multivitamin and mineral supplement, outcome: 7.3 mortality.

Sources of support

Internal sources

- National Health Service (NHS), UK
  All authors work in the NHS and receive salaries from the NHS

External sources

- Macmillan Cancer Care, UK
  SB is supported by a Post Doctoral Fellowship from Macmillan Cancer Care

Feedback

Appendices

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. NURITIONAL 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

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

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.

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

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"

5 CINAHL (Ebsco) search strategy

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

6 mRCT search strategy

Search terms: bladder cancer, nutrition

7 NCI search strategy

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

8 ClinicalTrials.gov search strategy

Search terms: bladder cancer, nutrition

9 WHO ICTRP search strategy

Search terms: bladder cancer, nutrition

10 Zetoc search strategy

Search terms: bladder cancer, nutrition

11 WorldCatDissertations search strategy

Search terms: bladder cancer and nutrition