

Original Article: Clinical Investigation**Oncological and functional outcomes of postoperative total parenteral nutrition after radical cystectomy in bladder cancer patients: A single-center randomized trial**Alvaro Vidal,^{1,2,†} Nicolas Arnold,^{1,†} Mihai Dorin Vartolomei,^{1,3} Bernhard Kiss,¹ Fiona Burkhard,¹ George N Thalmann¹ and Beat Roth¹¹Department of Urology, University of Bern, Bern, Switzerland, ²Faculty of Medicine, University of Chile, Santiago, Chile, and³Department of Cell and Molecular Biology, University of Medicine and Pharmacy, Târgu-Mureș, Romania**Abbreviations & Acronyms**

BMI = body mass index
CSS = cancer-specific survival
ePLND = extended pelvic lymphadenectomy
FSFI = Female Sexual Function Index
GIQLI = Gastrointestinal Quality of Life Index
IIEF-15 = International Index of Erectile Function
OS = overall survival
RC = radical cystectomy
RFS = recurrence-free survival
SF-12/36 = Short Form health survey 12/36
TPN = total parenteral nutrition
UD = urinary diversion

Objectives: To prospectively evaluate the long-term oncological and functional outcomes of postoperative total parenteral nutrition after radical cystectomy.**Methods:** A total of 157 consecutive patients (\leq cT3, cN0, cM0) who underwent extended pelvic lymph node dissection, radical cystectomy and ileal urinary diversion from September 2008 to March 2011 at a single center were randomized to receive either postoperative total parenteral nutrition (group A; $n = 74$) or oral nutrition alone (group B; $n = 83$). All but two patients in group B (who were thus excluded from further analysis) had regular postoperative follow up at the Department of Urology, University of Bern, Switzerland. Computed tomography and bone scan were carried out to assess local recurrences and distal metastases. We used validated questionnaires to evaluate bowel function, sexual function and quality of life, and an institutional questionnaire to evaluate neobladder function.**Results:** The median follow up was 50 months (IQR 21–62). The rate of local recurrences (4/74 [5.4%] in group A; 4/81 [4.9%] in group B; $P = 0.9$) and the rate of distant metastases (23/74 [31%] in group A; 23/81 [28%] in group B; $P = 0.72$) did not differ between the two groups. There was no difference in cancer-specific ($P = 0.86$) and overall survival ($P = 0.85$). Group B patients had significantly better bowel function at 3 months ($P = 0.03$) and 12 months ($P = 0.01$). There was no difference in terms of quality of life, and sexual and neobladder function.**Conclusions:** The administration of total parenteral nutrition after radical cystectomy does not impair long-term oncological outcomes. It does, however, negatively influence long-term bowel function.**Key words:** bladder cancer, cystectomy, functional outcomes, oncological outcomes, parenteral nutrition.**Correspondence:** Beat Roth M.D., Department of Urology, University Hospital Bern, Effingerstrasse, CH-3010 Bern, Switzerland. Email: urology.berne@insel.ch

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Online publication 21 October 2016**Introduction**

Because protein depletion as a sign of postoperative catabolism appears rapidly after major surgery, TPN is often part of postoperative routine care after RC, especially in Europe, irrespective of malnutrition status or postoperative period of semistarvation.¹ This stands in contrast to the growing literature showing a negative impact of TPN on short-term postoperative cystectomy outcome.^{2–4} While Declercq *et al.*² showed that oral nutrition was associated with a decreased length of stay and costs in RC patients as compared with postoperative TPN, Roth *et al.*⁴ were able to show in a prospective randomized trial an increase in postoperative infectious complications in patients undergoing ePLND, RC and ileal UD if TPN was administered postoperatively. This is in line with the data of Pham *et al.* showing an increased risk of bacteremia after TPN.³ This increase in bacteremia and infectious complications is probably as a result of an impairment of the immune system.^{5,6} However, short-term TPN appears to have biochemical⁴ and clinical^{7,8} benefits in malnourished patients and in patients expected to have a delay in gastrointestinal recovery of >7 days. Yet no data exist regarding the influence of early adequate protein supplementation after RC on long-term functional results, such as quality of life, sexual, gastrointestinal and neobladder function. Furthermore, it is feared that the use of intravenous nutrients in cancer patients could be associated with stimulation of

both cancer growth and tumor progression, as repeatedly shown in animal studies.^{9,10} As the results of human studies on the impact of TPN on cancer growth and progression are conflicting and inconclusive, we assessed the impact of TPN versus oral alimentation alone on long-term oncological and functional outcomes in patients undergoing ePLND, RC and ileal UD.^{11–13}

Methods

Patients

A randomized, single-center, single-blinded, two-arm trial was carried out on 157 consecutive patients with bladder cancer (\leq cT3, cN0, cM0) who underwent RC, ePLND and ileal UD from September 2008 to March 2011. Patients were randomized using a computer-based program (without stratification) to receive either postoperative TPN (group A; $n = 74$) or oral nutrition alone (group B; $n = 83$). Exclusion criteria were previous radiation therapy to the pelvis or abdomen, prior bowel surgery, chronic inflammatory bowel disease, severe hepatic or cardiac dysfunction, cT4 bladder cancer and inability to give full informed consent. Preoperative patient characteristics did not differ between the two groups (Table 1). Patients were defined as malnourished if their body mass index was <18.5 , if they had experienced an involuntary weight loss $>10\%$ within the preceding 6 months and/or if their serum protein levels were low (albumin <30 g/L, serum pre-albumin <0.2 g/L and/or total serum protein <60 g/L). Findings of the preoperative nutrition status screening had no influence on pre-, peri- and postoperative management. Two patients in group B (both malnourished preoperatively) did not have follow up at the Department of Urology, University of Bern, Switzerland, and thus were excluded from analysis (Fig. 1). The study was based on good clinical practice, and the Ethics Committee of the Canton of Bern, Switzerland (Kantonale Ethikkommission), gave its approval for this study (protocol number 160/10), which has therefore been carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. All patients gave their informed consent before their inclusion in the study. This trial was registered at www.isrctn.com (ISRCTN79535150).

Patient management

We previously described the surgical technique and patient management in detail.⁴ Briefly, surgery started with a standardized ePLND encompassing the internal, external and common iliac lymph nodes up to the uretero-iliac junction, and the obturator fossa. Nerve sparing during cystectomy was attempted whenever possible, unilaterally on the non-tumor-bearing side for unilateral tumors and bilaterally for tumors located at the bladder dome or anterior bladder wall. The bowel anastomosis was carried out end-to-end. All patients had a combination of general and epidural anesthesia intraoperatively. Epidural analgesia consisting of bupivacaine hydrochloride, fentanyl citrate and adrenaline was given postoperatively. Intraoperative fluid administration was restricted. Patients were given low-molecular-weight heparin subcutaneously into the arm to prevent thrombosis.

Table 1 Patient characteristics

| | Group A with parenteral nutrition ($n = 74$) | Group B with oral nutrition alone ($n = 83$) | P-value |
|--------------------------------------|--|--|---------|
| Median age, years (range) | 67 (34–80) | 66 (30–86) | 0.8 |
| Sex, n (%) | | | 0.5 |
| Male | 51 (69) | 53 (64) | |
| Female | 23 (31) | 30 (36) | |
| Median BMI (range) | 25.5 (17.7–35.2) | 26 (17.2–40.2) | 0.6 |
| Malnutrition, n (%) | 11 (15) | 23 (28) | 0.1 |
| Kondrup score, n (%) | | | 0.3 |
| II | 39 (53) | 34 (41) | |
| III | 31 (42) | 37 (45) | |
| IV | 3 (4) | 10 (12) | |
| V | 0 (0) | 1 (1) | |
| VI | 1 (1) | 1 (1) | |
| Neoadjuvant chemotherapy, n (%) | 12 (16) | 18 (22) | 0.4 |
| Adjuvant chemotherapy, n (%) | 25 (27) | 21 (25) | 0.2 |
| Urinary diversion, n (%) | | | 0.5 |
| Ileal conduit | 18 (24) | 23 (28) | |
| Orthotopic bladder substitute | 51 (69) | 51 (61) | |
| Catheterizable pouch | 5 (7) | 9 (11) | |
| Tumor stage, n (%) | | | 0.5 |
| pTis/pTa | 4 (5) | 6 (7) | |
| pT1 | 13 (18) | 21 (25) | |
| pT2 | 25 (34) | 27 (33) | |
| pT3 | 24 (32) | 25 (30) | |
| pT4 | 8 (11) | 4 (5) | |
| Lymph node involvement, n (%) | | | 0.3 |
| pN0 | 46 (62) | 58 (70) | |
| pN+ | 28 (38) | 25 (30) | |
| Median time for surgery, min (range) | 403 (240–500) | 400 (300–800) | 0.5 |
| Nerve sparing, n (%) | | | 0.7 |
| No | 21 (28) | 26 (31) | |
| Yes | 53 (72) | 57 (69) | |
| Unilateral | 28 (38) | 31 (37) | |
| Bilateral | 25 (34) | 26 (31) | |
| Seminal vesicle sparing, n (%) | | | 0.9 |
| No | 36 (71) | 38 (72) | |
| Yes (unilateral/bilateral) | 15 (29) | 15 (28) | |

Kondrup score, nutritional risk screening score according to the ESPEN Guidelines for Nutrition Screening 2002.

Nutrition management

No specific preoperative nutrition was given. Group A patients were given TPN consisting of Nutriflex special 70/240 (B. Braun Medical, Melsungen, Germany) with a total energy of 1240 kcal/L, and containing polyamino acids, glucose and electrolytes (1500 mL/24 h continuously) for 5 days starting within 24 h after surgery. Additionally, 30 IU human insulin and 1875 IU heparin were added to the TPN solution. No lipids, trace elements or

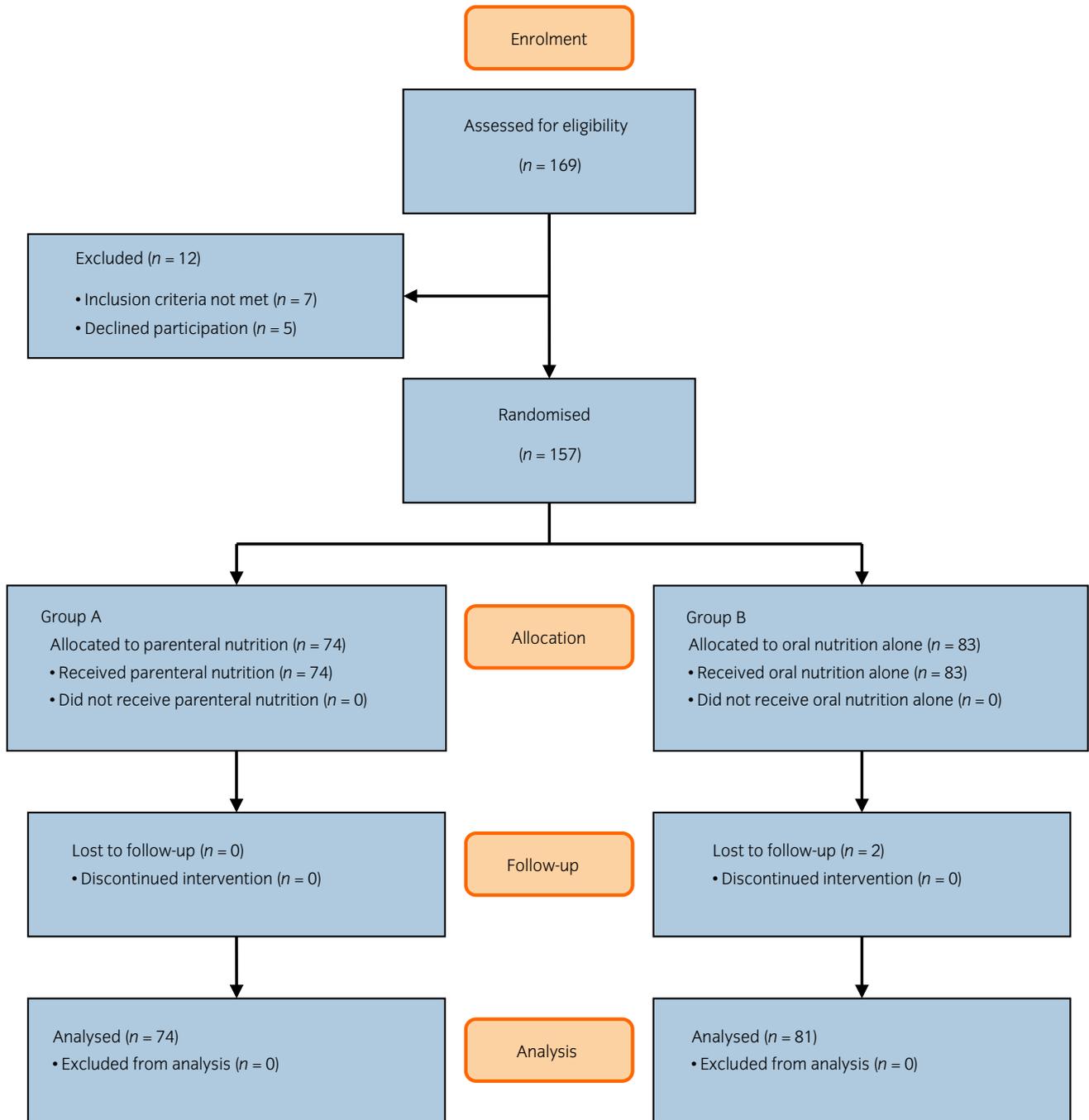


Fig. 1 Consort diagram showing the number of patients who were randomly assigned, treated and analyzed.

vitamins were administered systemically. Group B patients were given 1500 mL/24 h Ringer’s lactate solution with additional potassium substitution (40 mmol/24 h). An additional 1000 mL/24 h glucose 5% solution was administered to all patients in both groups for the first 5 postoperative days. Because all patients had a gastrostomy tube in place, which was initially left on drainage, oral intake was started on the day of surgery (fluids: water, tea, broth) in all patients of both groups. A solid diet was introduced on the return of active bowel sounds and gradually advanced as tolerated.

Outcome measures

The trial was originally designed to evaluate early postoperative complications (≤30 days following surgery) as the primary end-point. Secondary end-points included oncological and functional outcomes in the short- and long-term.⁴ Short-term (≤30 days after surgery) results were already published in 2012 showing that group B with oral nutrition alone had fewer early complications and less nausea as a sign of an improved early recovery of bowel function.⁴ In the present study, we report the long-term follow up of this trial.

Follow up

Patients had regular follow up at our outpatient clinic according to our institutional follow-up protocol 3, 6, 12, 18, 24, 30 and 36 months after surgery, and annually thereafter, as described in detail before.¹⁴ Computed tomography and bone scan (carried out at 6, 12 and 24 months, and if clinically indicated) were part of the clinical follow up. A local recurrence was defined as a soft tissue mass ≥ 2 cm occurring inside the bony pelvis. Distant recurrences (metastases) were defined as those lesions occurring outside the pelvis. To evaluate functional outcome, patients were asked to respond to the following questionnaires at the time-points 0, 3, 12 and 24 months during follow up: the modified validated GIQLI questionnaire¹⁵ to assess gastrointestinal function (Table 2); the FSFI for women¹⁶ and the IIEF-15 for men¹⁷ to assess sexual function; the SF-12 health survey, a shorter form of the SF-36 health survey,¹⁸ to assess quality of life; and our institutional post-cystectomy neobladder outcome questionnaire to assess neobladder function in patients receiving a bladder substitute (Table S1).¹⁹

Statistical analysis

We used SPSS (version 17; Chicago, IL, USA) for statistical analysis. Graphics were created using GraphPad Prism 5 Software (GraphPad, San Diego, CA, USA). Data were labeled as nominal (characterized as means of frequencies) or quantitative variables. The Kolmogorov–Smirnov test was applied to test quantitative variables for normality of distribution. Quantitative variables were described as mean \pm SD, or median (\pm range or IQR range), whichever was appropriate, for the GIQLI, FSFI, IIEF-15, SF-36 and institutional neobladder questionnaires. The Kruskal–Wallis test with Dunn's multiple comparison was used to analyze differences in the median values between groups. The χ^2 -test was used to compare frequencies of nominal variables. The Kaplan–Meier method was used for survival analysis, and the log-rank test for univariate comparisons. A *P*-value < 0.05 was considered as statistically significant. Assuming complication rates in group A and B of 20% and 36.7%, respectively, and based on a one-sided Fisher exact test with a significance level of 5% ($\alpha = 0.05$) and a power of 80% ($\beta = 0.2$), a sample size of $n = 100$ for each group was initially calculated. Because infectious complications in group A with TPN were more frequent than anticipated, the study was terminated before enrolment targets were met.⁴

Results

Survival outcome

The median follow up was 50 months (IQR 21–62). OS ($P = 0.85$) and CSS ($P = 0.86$) did not differ between the two groups: 5-year OS rates were 62% and 59%, and 5-year CSS rates were 68% and 68% in groups A and B, respectively (Fig. 2a,b). There was also no significant difference in the rate of local (pelvic) recurrence (4/74 [5.4%] in group A; 4/81 [4.9%] in group B; $P = 0.9$) and the rate of distant metastases (23/74 [31%] in group A; 23/81 [28%] in

group B; $P = 0.72$). RFS ($P = 0.78$; Fig. 2c) and local (pelvic) RFS ($P = 0.96$; Fig. 2d) did not differ between the two groups: RFS rates at 1 year were 77% and 78%, and at 5 years were 61% and 64% for groups A and B, respectively (Fig. 2c). Subgroup analysis showed a significant difference in OS ($P = 0.044$) and CSS ($P = 0.038$) between preoperatively malnourished ($n = 32$) versus non-malnourished ($n = 123$) patients (Fig. 3a,b), which was independent of tumor stage. There was, however, no difference in OS ($P = 0.9$) and CSS ($P = 0.7$) between group A ($n = 11$) and group B ($n = 21$) malnourished patients.

Functional outcome

The GIQLI questionnaire analysis showed a statistically significant difference between the two groups in terms of abdominal pain (*Q1*; at 12 months), burping/belching (*Q3*; at 3 months) and diarrhea (*Q5*; at 3 months), with patients in group B receiving oral alimentation alone having more favorable postoperative outcomes (Table 2). Postoperative neobladder function did not differ between the two groups, except for urinary urgency (*Q12a*) after 12 months in favor of group A (with TPN; Table S1). There was no difference between the two groups in terms of quality of life (SF-12; Table S2) and sexual function (FSFI, IIEF-15; Table S2). However, erectile function was significantly better if nerve sparing (unilaterally or bilaterally) was carried out ($P = 0.02$ and 0.012 compared with no nerve sparing at 12 and 24 months, respectively); erectile function was even better after additional seminal vesicle sparing (unilaterally or bilaterally; $P = 0.004$ and 0.006 compared with no seminal vesicle sparing at 12 and 24 months, respectively).

Discussion

The prevalence of malnutrition with or without cancer cachexia is high among patients with cancer, including bladder cancer patients who are candidates for RC and UD.²⁰ As weight loss and malnutrition are well-recognized risk factors for increasing morbidity and mortality rates in cancer patients,²¹ TPN is often part of postoperative routine care after RC – especially in Europe – irrespective of preoperative nutrition status and the postoperative (semi)starvation period.¹ The present randomized study shows that there is no benefit from non-selective postoperative parenteral alimentation after RC over oral alimentation alone in terms of long-term survival and functional outcomes; indeed, gastrointestinal function seems to be impaired by TPN.

Postoperative ileus with consequent delay in resuming natural feeding is a frequent complication after RC and UD, occurring in up to 26% of cystectomy patients.²² As it is recommended that artificial nutrients should be provided if (semi)starvation lasts for > 7 –10 days, parenteral nutrition is often the only possible way to administer nutrition in these patients.^{8,23} The fear exists, however, that parenteral nutrition “feeds” not only the cancer patient, but also the cancer itself. Indeed, animal studies have repeatedly shown that intravenous nutrients can stimulate both cancer growth and metastasis.^{9,10} Results in humans, however, are conflicting. In a

Table 2 GIQLI Questionnaire

| How often during the past 2 weeks have you been troubled by: | 0 month | | 3 months | | 12 months | | 24 months | |
|--|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | Group A n = 43 | Group B n = 43 | Group A n = 33 | Group B n = 30 | Group A n = 30 | Group B n = 26 | Group A n = 25 | Group B n = 24 |
| Q1: Stomach aches (%) | | | | | | | | |
| All the time (0) | 2.4 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Most of the time (1) | 0.0 | 0.0 | 3.1 | 0.0 | 3.2 | 0.0 | 4.2 | 0.0 |
| Sometimes (2) | 21.4 | 7.0 | 9.4 | 16.7 | 14.3 | 23.1 | 20.8 | 13.0 |
| Rarely (3) | 23.8 | 14.0 | 18.8 | 33.3 | 39.5 | 7.7 | 20.8 | 34.8 |
| Never (4) | 52.4 | 79.0 | 68.8 | 50.0 | 43.0 | 69.2 | 54.2 | 52.2 |
| P-value | 0.04 | | 0.28 | | 0.01 | | 0.77 | |
| Q2: Flatulence (%) | | | | | | | | |
| All the time (0) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.8 | 0.0 | 0.0 |
| Most of the time (1) | 2.4 | 2.3 | 6.3 | 3.3 | 0.0 | 0.0 | 8.3 | 0.0 |
| Sometimes (2) | 19.0 | 18.6 | 9.4 | 26.7 | 17.9 | 34.6 | 16.7 | 21.7 |
| Rarely (3) | 23.8 | 23.3 | 34.3 | 23.3 | 35.7 | 26.9 | 25.0 | 30.5 |
| Never (4) | 54.8 | 55.8 | 50.0 | 46.7 | 46.4 | 34.6 | 50.0 | 47.8 |
| P-value | 0.90 | | 0.35 | | 0.25 | | 0.81 | |
| Q3: Burping/belching (%) | | | | | | | | |
| All the time (0) | 0.0 | 0.0 | 3.2 | 0.0 | 0.0 | 0 | 0.0 | 0.0 |
| Most of the time (1) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Sometimes (2) | 7.2 | 0.0 | 0.0 | 3.3 | 0.0 | 3.8 | 13.0 | 4.4 |
| Rarely (3) | 7.2 | 11.9 | 12.9 | 0.0 | 14.3 | 3.8 | 17.4 | 8.7 |
| Never (4) | 85.6 | 88.1 | 83.9 | 96.7 | 85.7 | 92.4 | 69.6 | 87.0 |
| P-value | 0.33 | | 0.04 | | 0.21 | | 0.50 | |
| Q4: Fecal urgency (%) | | | | | | | | |
| All the time (0) | 0.0 | 0.0 | 3.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Most of the time (1) | 4.8 | 2.4 | 0.0 | 0.0 | 0.0 | 3.8 | 4.2 | 0.0 |
| Sometimes (2) | 9.5 | 11.9 | 19.4 | 13.3 | 21.4 | 11.5 | 12.5 | 18.2 |
| Rarely (3) | 35.7 | 28.6 | 35.5 | 30.0 | 42.9 | 42.3 | 50.0 | 31.8 |
| Never (4) | 49.9 | 57.2 | 42.0 | 56.7 | 35.7 | 42.3 | 33.3 | 49.9 |
| P-value | 0.90 | | 0.44 | | 0.50 | | 0.55 | |
| Q5: Diarrhea (%) | | | | | | | | |
| All the time (0) | 2.5 | 0.0 | 6.5 | 0.0 | 0.0 | 0.0 | 4.2 | 0.0 |
| Most of the time (1) | 0.0 | 0.0 | 0.0 | 3.3 | 4.1 | 3.8 | 4.2 | 0.0 |
| Sometimes (2) | 15.1 | 7.2 | 25.8 | 6.7 | 14.2 | 23.1 | 16.7 | 13.0 |
| Rarely (3) | 22.5 | 21.4 | 12.9 | 30.0 | 32.0 | 34.6 | 12.5 | 39.1 |
| Never (4) | 55.8 | 71.4 | 54.8 | 60 | 49.8 | 38.5 | 62.5 | 47.8 |
| P-value | 0.46 | | 0.03 | | 0.66 | | 0.33 | |
| Q6: Constipation (%) | | | | | | | | |
| All the time (0) | 2.5 | 2.5 | 3.2 | 0.0 | 0.0 | 0.0 | 0.0 | 4.4 |
| Most of the time (1) | 5.0 | 7.5 | 6.5 | 0.0 | 7.7 | 0.0 | 9.5 | 0.0 |
| Sometimes (2) | 10.0 | 17.5 | 16.2 | 14.3 | 3.8 | 3.8 | 9.5 | 17.4 |
| Rarely (3) | 17.5 | 17.5 | 29.0 | 28.6 | 30.8 | 34.6 | 38.1 | 26.1 |
| Never (4) | 65.0 | 55.0 | 45.1 | 57.1 | 57.7 | 61.7 | 42.9 | 52.1 |
| P-value | 0.93 | | 0.75 | | 0.21 | | 0.30 | |
| Q7: Nausea (%) | | | | | | | | |
| All the time (0) | 0.0 | 0.0 | 3.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Most of the time (1) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Sometimes (2) | 4.8 | 2.4 | 9.7 | 0.0 | 7.4 | 3.8 | 17.4 | 4.4 |
| Rarely (3) | 16.7 | 9.8 | 9.7 | 10.3 | 25.9 | 7.7 | 8.7 | 8.7 |
| Never (4) | 78.5 | 87.8 | 77.3 | 89.7 | 66.7 | 88.5 | 73.9 | 87.0 |
| P-value | 0.67 | | 0.47 | | 0.08 | | 0.53 | |
| Q8: Stool incontinence (%) | | | | | | | | |
| All the time (0) | 0.0 | 0.0 | 3.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Most of the time (1) | 0.0 | 0.0 | 0.0 | 0.0 | 3.8 | 0.0 | 9.1 | 0.0 |
| Sometimes (2) | 4.8 | 0.0 | 3.2 | 0.0 | 0.0 | 0.0 | 13.6 | 4.4 |
| Rarely (3) | 7.2 | 10.0 | 9.7 | 3.4 | 11.5 | 3.8 | 9.1 | 4.4 |
| Never (4) | 88.0 | 90.0 | 83.9 | 96.6 | 84.6 | 96.2 | 68.2 | 91.2 |
| P-value | 0.49 | | 0.64 | | 0.10 | | 0.28 | |

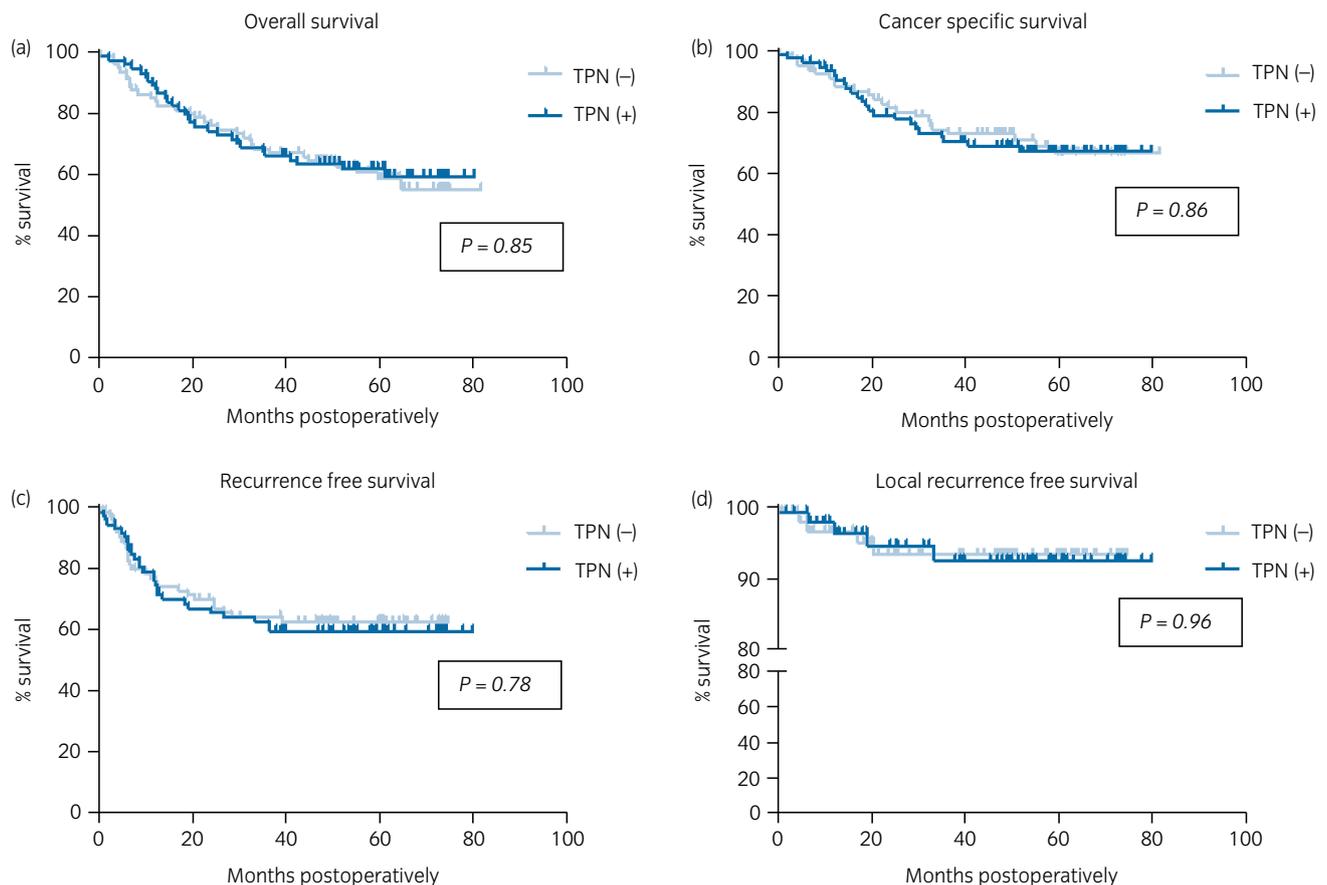


Fig. 2 Survival curves comparing patients receiving parenteral nutrition [TPN (+); group A] and patients receiving oral nutrition alone [TPN (-); group B].

review, Bozzetti *et al.* could show in seven out of 12 human studies of patients with head and neck or gastrointestinal cancer that parenteral nutrition induced cancer growth, whereas no cancer growth was observed in control cancer patients who followed a standard oral diet.¹¹ Still, Bozzetti *et al.* concluded that there is a lack of evidence that parenteral nutrition's possible stimulation of cancer growth translates into clinically relevant harm to the patient, which is in line with our data showing no difference in CSS between the groups with and without TPN after RC and UD.¹¹ Indeed, current guidelines recommend that fear of tumor growth as a result of administration of artificial nutrition should not hamper the decision to initiate artificial nutrition when its use is indicated on clinical grounds; for example, if (semi)starvation lasts for >7–10 days.^{8,24}

Malnutrition is a frequent problem in patients undergoing RC and UD. Jensen *et al.* reported 26% of cystectomy patients to be at nutritional risk preoperatively, which is in line with our cohort of cystectomy patients, 22% (34/157) of whom were malnourished preoperatively.²⁵ This is important because malnutrition is a relevant factor for worse outcome after RC and UD.²⁵ Indeed, the present subgroup analysis showed a significantly decreased OS and CSS in the preoperatively malnourished group (Fig. 3): 5-year OS was 64% for preoperatively non-malnourished patients versus 45% for preoperatively malnourished patients. This difference was mainly

as a result of more deaths in the malnourished group occurring within the first 12 months postoperatively: 1-year OS was 96% in the non-malnourished and 81% in the malnourished group of cystectomy patients. While postoperative parenteral nutrient supplementation might appear an ideal strategy to control and reverse malnutrition, several clinical trials failed to show a positive effect in reversing or controlling weight loss in cancer patients.¹³ Indeed, we could not show a difference between group A and B malnourished patients in terms of oncological or functional outcomes. Although the present study was underpowered for this subgroup analysis, the complex nature of cancer cachexia and malnutrition – a chronic wasting syndrome characterized by an uncoupling between nutrient provision and tissue anabolism resulting in progressive muscle depletion with or without fat mass – is most probably the reason why administration of postoperative TPN alone does not necessarily lead to a better outcome if malnutrition is present.²⁶ Furthermore, providing nutritional support parenterally without paying attention to the patients' nutritional status might even negatively influence patients' outcome (e.g. because of the negative impact on the immune system by altering the monocyte tumor necrosis factor receptor activity, which in turn increases susceptibility to infection).¹³

As optimization of metabolic state before major surgery leads to improved surgical outcomes, the question arises

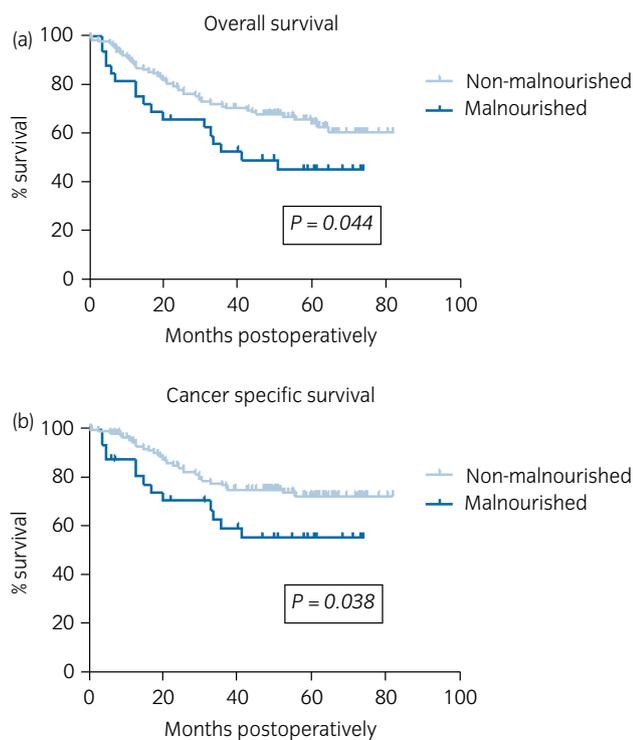


Fig. 3 Survival curves comparing the malnourished ($n = 32$) and non-malnourished ($n = 123$) subgroup of patients.

whether prehabilitation including administration of nutritional supplements rich in proteins and calories can beneficially impact outcome after RC and UD, especially in malnourished patients. In a randomized trial, Jensen *et al.* could show that a preoperative (and postoperative) rehabilitation program did not reduce complications and the length of hospitalization, although enhanced mobilization was achieved.²⁷ Still, the study was underpowered to show significant differences in postoperative complications (total $n = 107$), especially because just 26% of patients were at nutritional risk and therefore most likely to benefit from a preoperative rehabilitation program. Whether additionally providing supplements that improve the immune function (specialized immunonutrition including e.g. L-arginine, fish oil, vitamin A and dietary nucleotides derived from yeast RNA, as recently proposed in a small pilot study²⁸) needs to be evaluated in adequately sized clinical trials.

Although no significant difference in time to recovery of bowel function after surgery was noticed, patients with postoperative TPN had worse gastrointestinal function 3 months and 12 months after RC, as compared with orally nourished patients.⁴ This is in line with the findings of others showing a negative impact of long-lasting TPN on long-term bowel function.²⁹ The reason for this difference, however, is not fully clear, as the lack of enteral stimulation for several days should not be enough time to establish changes in the structure and function of the gut.

Postoperative TPN did not impact neobladder or sexual function, which suggests that administration of nutritional supplements does not influence nerve rehabilitation after surgical trauma. However, nerve sparing (unilaterally or

bilaterally) and seminal vesicle sparing had a significant impact on sexual function, with patients having better postoperative erectile function after nerve sparing as compared with patients in whom nerve sparing was not feasible.

A limitation of the present study was that it had to be stopped early because of a relevant increase in (infectious) complications in group A patients receiving TPN.⁴ Another potential limitation is that the TPN we used contained only polyamino acids, glucose and electrolytes, but no lipids. Lipids, however, have been shown to negatively impact clinical outcomes by negatively affecting the immune system, which is why we used standard TPN without lipids.³⁰

In conclusion, the administration of TPN does not impair long-term oncological outcomes after ePLND, RC and UD. Postoperative TPN, however, appears to negatively influence long-term bowel function. Therefore, it should only be given to a highly selected cohort of patients; for example, patients with a prolonged ileus and a (semi)starvation period of >7–10 days. Although malnutrition is a parameter of poor postoperative outcome, we could not show that postoperative TPN had any benefit over oral alimentation alone in the malnourished group of patients. Combined preoperative and postoperative rehabilitation programs will have to be evaluated in order to improve the outcome of malnourished patients after RC and UD.

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Conflict of interest

None declared.

References

- Barrass BJ, Thurairaja R, Collins JW, Gillatt D, Persad RA. Optimal nutrition should improve the outcome and costs of radical cystectomy. *Urol. Int.* 2006; **77**: 139–42.
- Declercq P, De Win G, Van der Aa F *et al.* Reduced length of stay in radical cystectomy patients with oral versus parenteral post-operative nutrition protocol. *Int. J. Clin. Pharm.* 2015; **37**: 379–86.
- Pham KN, Schwartz LW, Garg T *et al.* Immediate total parenteral nutrition after radical cystectomy and urinary diversion. *WJM* 2014; **113**: 20–3.
- Roth B, Birkhäuser FD, Zehnder P *et al.* Parenteral nutrition does not improve postoperative recovery from radical cystectomy: results of a prospective randomised trial. *Eur. Urol.* 2013; **63**: 475–82.
- Zaloga GP. Parenteral nutrition in adult inpatients with functioning gastrointestinal tracts: assessments of outcomes. *Lancet* 2006; **367**: 1101–11.
- Lin MT, Saito H, Fukushima R *et al.* Route of nutritional supply influences local, systemic, and remote organ responses to intraperitoneal bacterial challenge. *Ann. Surg.* 1996; **223**: 84–93.

- 7 Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critical ill patient: a meta-analysis. *JAMA* 1998; **280**: 2013–9.
- 8 Braga M, Ljungqvist O, Soeters P *et al*. ESPEN guidelines on parenteral nutrition: surgery. *Clin. Nutr.* 2009; **28**: 378–86.
- 9 Cameron IL, Pavlat WA. Stimulation of growth of a transplantable hepatoma in rats by parenteral nutrition. *J. Natl Cancer Inst.* 1976; **56**: 597–602.
- 10 Popp MB, Kirkemo AK, Morrison SD, Brennan MF. Tumour and host carcass changes during total parenteral nutrition in an anorectic rat-tumour system. *Ann. Surg.* 1984; **199**: 205–10.
- 11 Bozzetti F, Mori V. Nutritional support and tumour growth in humans: a narrative review of the literature. *Clin. Nutr.* 2009; **28**: 226–30.
- 12 Torosian MH, Daly JM. Nutritional support in the cancer-bearing host. Effects on host and tumor. *Cancer* 1986; **58**: 1915–29.
- 13 Muscaritoli M, Molino A, Laviano A, Rasio D, Rossi Fanelli F. Parenteral nutrition in advanced cancer patients. *Crit. Rev. Oncol. Hematol.* 2012; **84**: 26–36.
- 14 Giannarini G, Kessler TM, Thoeny HC, Nguyen DP, Meissner C, Studer UE. Do patients benefit from routine follow-up to detect recurrences after radical cystectomy and ileal orthotopic bladder substitution? *Eur. Urol.* 2010; **58**: 486–94.
- 15 Eypasch E, Williams JI, Wood-Dauphinee S *et al*. Gastrointestinal Quality of Life Index: development, validation and applications of a new instrument. *Br. J. Surg.* 1995; **82**: 216–22.
- 16 Kim DY, Choi JD. Change of sexual function after midurethral sling procedure for stress urinary incontinence. *Int. J. Urol.* 2008; **15**: 716–9.
- 17 Rosen RC, Riley A, Wagner G *et al*. The International Index of Erectile Function (IIEF): a multidimensional scale for the assessment of erectile dysfunction. *Urology* 1997; **49**: 822–30.
- 18 Jenkinson C, Layte R. Development and testing of the UK SF-12 (Short Form Health Survey). *J. Health Serv. Res. Policy* 1997; **2**: 14–8.
- 19 Madersbacher S, Moehrle K, Burkhard F, Studer UE. Long-term voiding pattern of patients with ileal orthotopic bladder substitutes. *J. Urol.* 2002; **167**: 2052–7.
- 20 Fearon KC. Cancer cachexia: developing multimodal therapy for a multidimensional problem. *Eur. J. Cancer* 2008; **44**: 1124–32.
- 21 Vigano A, Donaldson N, Higginson IJ, Bruera E, Mahmud S, Suarez-Almazor M. Quality of life and survival prediction in terminal cancer patients: a multicenter study. *Cancer* 2004; **101**: 1090–8.
- 22 Sabsigh A, Korets R, Vora KC *et al*. Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. *Eur. Urol.* 2009; **55**: 164–74.
- 23 ASPEN Board of Directors and the Clinical Guidelines Task Force. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *J. Parenter. Enteral Nutr.* 2002; **26** (Suppl 1): 1–138SA.
- 24 Bozzetti F, Arends J, Lundholm K *et al*. ESPEN guidelines on parenteral nutrition: non-surgical oncology. *Clin. Nutr.* 2009; **28**: 445–54.
- 25 Jensen BT, Laustsen S, Petersen AK *et al*. Preoperative risk factors related to bladder cancer rehabilitation: a registry study. *Eur. J. Clin. Nutr.* 2013; **67**: 917–21.
- 26 Penet MF, Bhujwala ZM. Cancer cachexia, recent advances, and future directions. *Cancer J.* 2015; **21**: 117–22.
- 27 Jensen BT, Petersen AK, Jensen JB, Laustsen S, Borre M. Efficacy of a multiprofessional rehabilitation programme in radical cystectomy pathways: a prospective randomized controlled trial. *Scand. J. Urol.* 2015; **49**: 133–41.
- 28 Hamilton-Reeves JM, Bechtel MD, Hand LK *et al*. Effects of immunonutrition for cystectomy on immune response and infection rates: a pilot randomized controlled clinical trial. *Eur. Urol.* 2016; **69**: 389–92.
- 29 Guglielmi FW, Boggio-Bertinet D, Federico A *et al*. Total parenteral nutrition-related gastroenterological complications. *Dig. Liver Dis.* 2006; **38**: 623–42.
- 30 Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N. Engl. J. Med.* 1990; **323**: 301–8.

Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Table S1. Postoperative neobladder function questionnaire.

Table S2. Quality of life (SF-12) and sexual function (FSFI, IIEF-15) questionnaires.