# ANESTHESIOLOGY

## Goal-directed *versus* Standard Fluid Therapy to Decrease Ileus after Open Radical Cystectomy

### A Prospective Randomized Controlled Trial

Vittoria Arslan-Carlon, M.D., Kay See Tan, Ph.D., Guido Dalbagni, M.D., Alessia C. Pedoto, M.D., Harry W. Herr, M.D., Bernard H. Bochner, M.D., Eugene K. Cha, M.D., Timothy F. Donahue, M.D., Mary Fischer, M.D., S. Machele Donat, M.D.

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### EDITOR'S PERSPECTIVE

#### What We Already Know about This Topic

- Postoperative ileus is a common complication after intraabdominal surgeries
- Previous studies have found mixed evidence for benefit in goal-directed intraoperative fluid therapy over standard fluid therapy

#### What This Article Tells Us That Is New

- In a randomized trial of goal-directed *versus* standard fluid therapy in patients having radical cystectomy, there was no difference in the primary outcome of postoperative ileus
- There was no difference between fluid therapies in the secondary outcome of high-grade complications

## ABSTRACT

**Background:** Postoperative ileus is a common complication of intraabdominal surgeries, including radical cystectomy with reported rates as high as 32%. Perioperative fluid administration has been associated with improvement in postoperative ileus rates, but it is difficult to generalize because earlier studies lacked standardized definitions of postoperative ileus and other relevant outcomes. The hypothesis was that targeted individualized perioperative fluid management would improve postoperative ileus in patients receiving radical cystectomy.

**Methods:** This is a parallel-arm, double-blinded, single-center randomized trial of goal-directed fluid therapy *versus* standard fluid therapy for patients undergoing open radical cystectomy. The primary outcome was postoperative ileus, and the secondary outcome was complications within 30 days post-surgery. Participants were at least 21 yr old, had a maximum body mass index of 45 kg/m$^2$ and no active atrial fibrillation. The intervention in the goal-directed therapy arm combined preoperative and postoperative stroke volume optimization and intraoperative stroke volume variation minimization to guide fluid administration, using advanced hemodynamic monitoring.

**Results:** Between August 2014 and April 2018, 283 radical cystectomy patients (142 goal-directed fluid therapy and 141 standard fluid therapy) were included in the analysis. Postoperative ileus occurred in 25% (36 of 142) of patients in the goal-directed fluid therapy arm and 21% (30 of 141) of patients in the standard arm (difference in proportions, 4.1%; 95% CI, −5.8 to 13.9; $P = 0.418$). There was no difference in incidence of high-grade complications between the two arms (20 of 142 [14%] *vs.* 23 of 141 [16%]; difference in proportions, −2.2%; 95% CI, −10.6 to 6.1; $P = 0.602$), with the exception of acute kidney injury, which was more frequent in the goal-directed fluid therapy arm (56% [80 of 142] *vs.* 40% [56 of 141] in the standard arm; difference in proportions, 16.6%; 95% CI, 5.1 to 28.1; $P = 0.005$; $P = 0.170$ after adjustment for multiple testing).

**Conclusions:** Goal-directed fluid therapy may not be an effective strategy for lowering the risk of postoperative ileus in patients undergoing open radical cystectomy.

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Postoperative ileus is a common complication affecting patients after intraabdominal surgery,[1,2] including radical cystectomy, for which the rate has been reported in the range of 2 to 32%.[3] Postoperative ileus can prolong hospitalization; therefore multiple studies have evaluated potential risk factors and perioperative and intraoperative care pathways to find preventative interventions. Most studies evaluating postoperative ileus in radical cystectomy have been retrospective.[4,5]

Individualized goal-directed fluid therapy guided by patient hemodynamic values seems to be the logical approach to avoid the extremes of fluid administration that can be associated with postoperative complications. However, data on the effect of goal-directed fluid therapy are still inconclusive, and even though some trials have shown benefits in outcome,[6–9] other trials have

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shown no benefit or even a negative impact on renal function.[10,11]

More recently, a large-scale randomized goal-directed fluid therapy study by Pearse *et al.*[10] included 734 patients undergoing major gastrointestinal surgery and did not show a statistically significant benefit for goal-directed fluid therapy; however, an updated meta-analysis including this population demonstrated benefit for goal-directed fluid therapy in preventing infectious complications in patients above the age of 65. The recently published, prospective, randomized study by Calvo-Vecino *et al.* (commonly known as FEDORA trial[9]) included 500 patients undergoing major elective abdominal surgery and showed that Doppler-guided goal-directed hemodynamic therapy reduced postoperative complications and hospital length of stay but did not show a difference in mortality.

The studies reported by Pillai *et al.*[12] and Wuethrich *et al.*[13] suggest that individualized goal-directed fluid therapy intraoperative fluid management in radical cystectomy patients may further reduce gastrointestinal and cardiac complications. Because our institution had already standardized postoperative care but intraoperative care was largely practitioner-dependent, we designed a three-part goal-directed fluid therapy algorithm combining stroke volume (SV) optimization and SV variation minimization to guide fluid administration during perioperative care for patients undergoing open radical cystectomy. Our hypothesis was that using goal-directed fluid therapy instead of our institution's standard care during open radical cystectomy would have an impact on postoperative ileus and perioperative outcomes.

## Materials and Methods

### Study Design and Participants

This double-blinded, prospective randomized trial was conducted under a Memorial Sloan Kettering Cancer Center Institutional Review Board–approved protocol (ClinicalTrials.gov NCT02145871; principal investigator, V. Arslan-Carlon; registration date, May 23, 2014; protocol can be accessed by request). All eligible patients with planned open radical cystectomy at Memorial Sloan Kettering Cancer Center were approached. Exclusion criteria included age less than 21 yr, active atrial fibrillation, and body mass index above 45 kg/m² because of the limitations of SV variation reading. Because of possible differences in complication rates between open and minimally invasive surgical approaches, the protocol was limited to patients undergoing open radical cystectomy.

### Randomization and Masking

A trained research assistant evaluated eligibility, written informed consent was obtained by a consenting professional, and patients were randomly assigned in a 1:1 ratio to the goal-directed fluid therapy or standard fluid therapy arm.

Randomization was performed *via* the Memorial Sloan Kettering Clinical Research Database using randomly sized permuted blocks; allocation was concealed by the database system. Patients and assessors of the primary outcome were blinded as to the study arm. Unblinding occurred after the trial was closed and data on all patients were collected.

### Procedures

*Preoperative and Intraoperative Care.* Patients in both arms received a radial artery catheter and were connected to an advanced hemodynamic monitor (EV1000 clinical platform *via* a Flotrac sensor; Edwards Lifesciences, USA). Treatment in the standard fluid therapy arm was based on Memorial Sloan Kettering historic fluid administration data for open radical cystectomy: maintenance of 10 ml · kg⁻¹ · h⁻¹ of balanced crystalloid solution (Normosol-R, ICU Medical Inc., USA) with blood loss replaced 1:1 with albumin 5% or packed red blood cells to maintain a hemoglobin level of at least 7 mg/dl.

Patients in the goal-directed fluid therapy arm underwent a passive leg raise in the operating room before induction to determine fluid responsiveness, based on SV augmentation of more than 10% (Supplemental Digital Content 1, preinduction algorithm, http://links.lww.com/ALN/C391). Patients with positive results from the passive leg raise were optimized with 250-ml balanced crystalloid boluses until their SV was no longer responsive. After induction, fluids were administered at 3 ml · kg⁻¹ · h⁻¹, and albumin 5% was administered to maintain SV variation less than 13% (Supplemental Digital Content 2, operating room algorithm, http://links.lww.com/ALN/C391); packed red blood cells were used instead of albumin to maintain a hemoglobin level of at least 7 mg/dl. No blood loss was replaced unless accompanied by an increase in SV variation.

All bowel anastomoses were stapled and performed in a standard side-to-side fashion using either a 60- or 80-mm gastrointestinal anastomosis stapler and a thoracoabdominal stapler. None of the anastomoses were hand-sewn.

In total, 225 patients received an epidural catheter; epidural infusion was started once specimen was removed. Infusions were standardized by the pain service and started at 6 ml/h of bupivacaine 0.05% with 8 µg/ml of hydromorphone; additional boluses of 6 ml every 30 min were permitted at the discretion of the anesthesia practitioner.

In the standard fluid therapy arm, the anesthesia team was blinded to the reading of the advanced hemodynamic monitor. To keep uniformity of procedures, the anesthesiologists participating in the trial were limited to four; if none were available, the patient was excluded from the study population as prespecified in the protocol.

*Postoperative Care.* All patients were transported to the postanesthesia care unit (PACU) unless the intensive care unit was indicated because of intraoperative events or preoperative comorbidities. The protocol fluid administration continued for the first 6 h in the PACU, with all patients in the standard fluid therapy arm receiving 1.5 ml · kg⁻¹ · h⁻¹ of

balanced crystalloid solution and those in the goal–directed fluid therapy arm receiving $1\,ml \cdot kg^{-1} \cdot h^{-1}$ of maintenance and any additional boluses given based on SV optimization. In cases of high potassium levels, balanced crystalloid solution was substituted with normal saline. All patients received colloid 250-ml boluses for systolic blood pressure less than 90 mmHg and/or urine output less than $0.5\,ml \cdot kg^{-1} \cdot h^{-1}$ over 2 h (Supplemental Digital Content 3, PACU algorithm, http://links.lww.com/ALN/C391). Patients were discharged from the PACU at the end of the 6-h protocol (or longer if required by preoperative comorbidities). On the floor, all patients were treated on our standardized postoperative enhanced recovery pathway (outline shown in Supplemental Digital Content 4, http://links.lww.com/ALN/C391), adjusted only as necessary for individual allergies, renal function, medical comorbidities, and acute medical events.

## Outcome Measures

The primary endpoint of postoperative ileus was defined as intolerance of oral intake by postoperative day 5, the cessation of diet, or placement of a nasogastric tube for clinical signs or symptoms associated with postoperative ileus, including one or more of the following: nausea, emesis, abdominal bloating or distension, or excessive burping.[5] In addition to separate causative *versus* secondary postoperative ileus we added: "primary postoperative ileus" as a gastrointestinal dysfunction that occurred in the absence of major grade 3 to 5 surgical or medical complications, defined based on the modified Clavien system.[5,14,15] Although this was not a protocol-specified endpoint, we defined and considered primary postoperative ileus as a secondary outcome before unblinding and data analysis. Protocol-defined secondary outcomes were total hospitalization fluid administration, blood transfusion rates, total dose of vasoactive agents, and pattern of overall and specific 30-day postoperative complications. Additional secondary outcomes were vasopressor use in the operating room, high-grade complications, and length of stay. Thirty-day complications were captured prospectively using the modified Clavien system[14] and the definitions described in our group's prior article.[5]

Renal function was assessed by both serum creatinine and calculated estimated glomerular filtration rate using both the Modification of Diet in Renal Disease and Chronic Kidney Disease Epidemiology Collaboration formulas; values were recorded at baseline (within 1 month before surgery) and at the time of hospital discharge, in addition to frequent serum creatinine evaluations during the hospitalization. We used the standard National Kidney Center classification system to describe the stages of chronic kidney disease.[16] For the purposes of the study, preexisting renal insufficiency was defined as baseline renal function less than 60 ml/min, consistent with stage 2 chronic kidney disease; the 60-ml/min cutoff is often used to determine whether patients are candidates for neoadjuvant chemotherapy.

## Statistical Analysis

All analyses were performed in a modified intention-to-treat population, which included all patients who had undergone both randomization and anesthesia with advanced hemodynamic monitoring for eligible surgery. All evaluable patients were followed for 30 days postoperatively, and none were lost to follow-up.

With a historical institutional postoperative ileus rate of 32%[17] and a two-sided type I error of 0.05, we calculated that 283 evaluable patients would provide 80% power to detect a 15% absolute difference in the proportions of patients with postoperative ileus between the two arms (hypothesized postoperative ileus rate of 17% in the goal-directed fluid therapy arm). This sample size also allowed for an interim analysis, using O'Brien–Fleming boundaries for both efficacy and futility. Pooled variance and the Casagrande–Pike–Smith continuity correction were utilized in the sample size calculation. The interim analysis was performed once the accrual reached 144 evaluable patients, but because it did not meet protocol-specified futility or efficacy thresholds, the trial continued to full enrollment.

The distributions of patient characteristics and outcomes were summarized as the number (proportion) for categorical factors and the median (interquartile range) for continuous factors. The primary outcome was proportion of patients with postoperative ileus within 30 days of operation, which was compared between the randomized arms using the chi-square test and quantified as the difference in proportions with the corresponding 95% CI. All binary secondary outcomes were assessed similarly. Secondary outcomes measured on a continuous scale were compared between the randomized arms using the Wilcoxon rank sum test and quantified as differences in means with corresponding 95% CI. A natural-log transformation was applied to outcomes that displayed a skewed distribution. In these instances, the estimated size of differences on the log scale were converted to the ratio of means on the original scale. The widths of the CI have not been adjusted for multiple testing, so the intervals should not be used for inference. No stratification was used in the analyses. Neither multivariable analyses to adjust for preoperative risk nor preplanned subgroup analyses were planned or performed.

Multiple testing was addressed by applying the Holm–Bonferroni adjustment to $P$ values from all secondary outcomes with a family-wise significance level of 0.049 to account for the interim analysis. Statistical tests are two-sided. Analyses were conducted with Stata 13.1 (StataCorp, USA).

## Results

### Patients

Between August 5, 2014, and April 9, 2018, 320 patients soon to undergo open radical cystectomy consented to the protocol and were randomized (fig. 1). Of the 320 patients,

**Fig. 1.** Consolidated Standards of Reporting Trials diagram of patient flow.
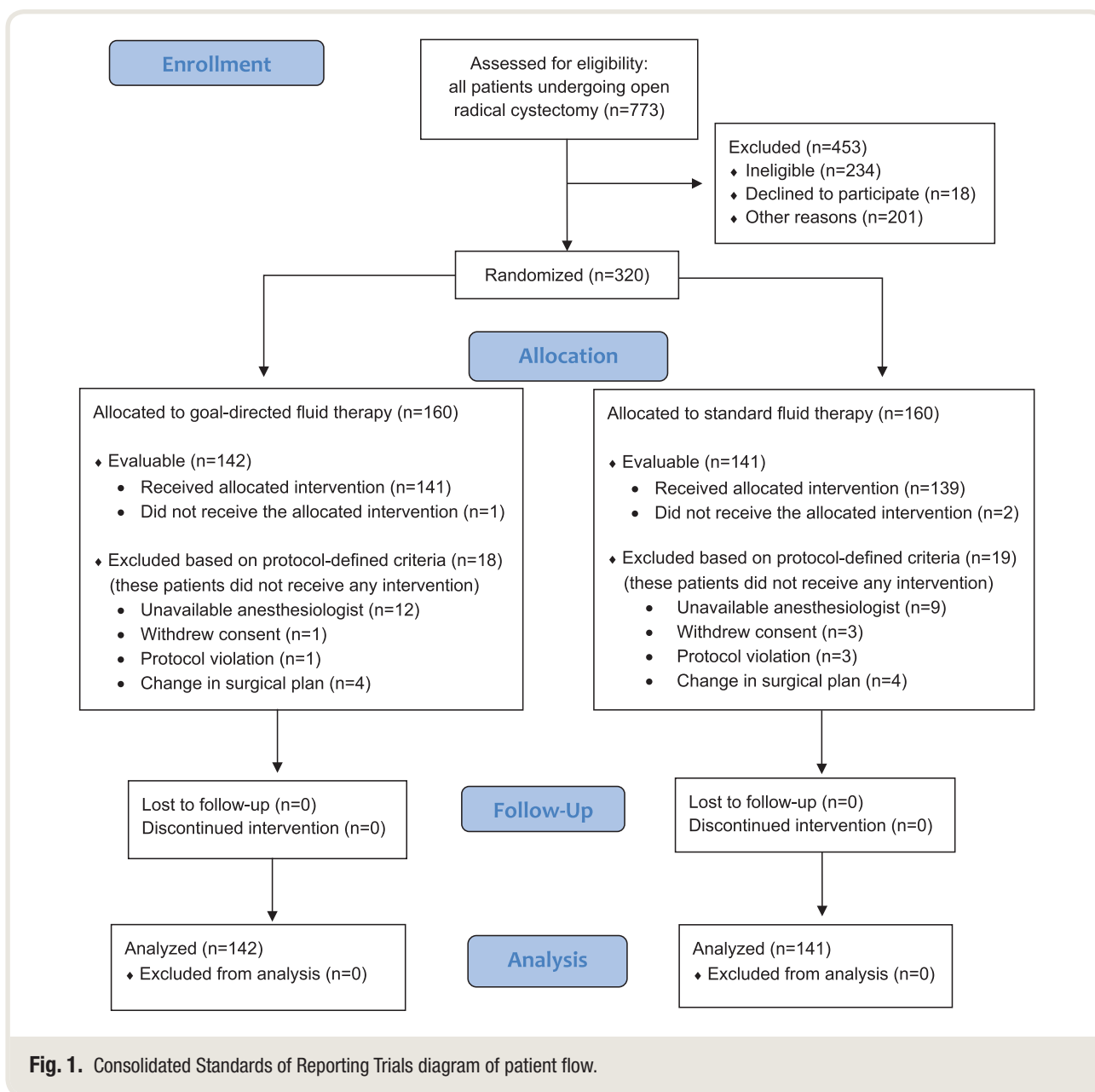
37 excluded after randomization based on protocol-defined exclusion criteria: 21 because of unavailability of participating anesthesiologists, 8 because of change in surgical plan, 4 patients withdrew consent, and 4 were found ineligible after consent because of atrial fibrillation on preoperative electrocardiogram. In total, 283 patients were considered evaluable and included in the analyses (142 in the goal-directed fluid therapy arm and 141 in the standard fluid therapy arm).

Baseline demographics, clinical characteristics, and preoperative risk factors for postoperative ileus were similar for both arms (table 1). Intraoperative characteristics are shown in table 2.

Fluid management (volume and type), weight differences and changes, and fluid balance characteristics are shown in

table 3. The goal-directed fluid therapy arm reported lower total fluid output (median [interquartile range]) than the standard fluid therapy arm (13,380 ml [10,405 to 19,093] *vs.* 15,445 ml [11,920 to 21,015]; $P = 0.044$) and higher colloid intake intraoperatively (1,000 ml [750 to 1,250] *vs.* 750 ml [500 to 1,000]; $P = 0.005$) although not over the whole protocol period, which included the 6 h of recovery (1,000 ml [750 to 1,500] *vs.* 975 ml [500 to 1,350]; $P = 0.053$). The goal-directed fluid therapy arm also had a lower intraoperative and 6-h recovery room crystalloid intake (median [interquartile range], 2,892 ml [2,340 to 3,450] *vs.* 5,580 ml [4,650 to 6,730]; $P < 0.0001$) than the standard arm. The total dose of intraoperative vasopressors (ephedrine or phenylephrine) was comparable between arms, similarly

**Table 1.** Demographic and Preoperative Characteristics of Patients

| Characteristics | Both Arms Combined (N = 283) | Goal-directed Fluid Therapy (N = 142) | Standard Fluid Therapy (N = 141) |
|---|---|---|---|
| Sex | | | |
|    Female | 62 (22%) | 30 (21%) | 32 (23%) |
|    Male | 221 (78%) | 112 (79%) | 109 (77%) |
| Age at surgery, yr | 69 (63–76) | 70 (63–77) | 69 (62–75) |
| Charlson Comorbidity Index (excluding 2 points for cancer) | 1 (0–2) | 1 (0–2) | 1 (0–2) |
| Charlson Comorbidity Index adjusted for age | 4 (3–6) | 5 (3–6) | 4 (3–6) |
| Anesthesia category (ASA score I—II* vs. ASA score III—IV): highest value between presurgical testing and preoperative day | | | |
|    I—II* | 85 (30%) | 44 (31%) | 41 (29%) |
|    III—IV | 198 (70%) | 98 (69%) | 100 (71%) |
| Body mass index at surgery | 28.7 (25.4–31.8) | 28.7 (25.0–32.0) | 28.7 (25.8–31.4) |
| Body mass index above 30 kg/m$^2$ (obesity) | 111 (39%) | 57 (40%) | 54 (38%) |
| Number of patients with renal insufficiency by estimated glomerular filtration rate less than 60 ml/min | 95 (34%) | 42 (30%) | 53 (38%) |
| Number of patients with abnormal creatinine | 48 (17%) | 20 (14%) | 28 (20%) |
| Preoperative albumin 5% less than 3 g/dl | 2 (0.7%) | 2 (1.4%) | 0 (0%) |
| Smoking within the 6 months before surgery | 34 (12%) | 14 (10%) | 20 (14%) |
| Number of pack-years (N = 282) | 15 (0–40) | 15 (0–40) | 15 (0–40) |
| History of COPD (emphysema, asthma, chronic bronchitis) | 46 (16%) | 29 (20%) | 17 (12%) |
| History of coronary artery disease | 58 (20%) | 37 (26%) | 21 (15%) |
| Myocardial infarction in past | 16 (5.7%) | 12 (8.5%) | 4 (2.8%) |
| Longstanding arrhythmia | 9 (3.2%) | 7 (4.9%) | 2 (1.4%) |
| Prior venous embolic event (deep vein thrombosis, pulmonary embolism) | 36 (13%) | 16 (11%) | 20 (14%) |
| Non–insulin-dependent diabetes | 49 (17%) | 24 (17%) | 25 (18%) |
| Insulin-dependent diabetes | 12 (4.2%) | 6 (4.2%) | 6 (4.3%) |
| Diabetes-related peripheral neuropathy | 6 (2.1%) | 3 (2.1%) | 3 (2.1%) |
| Hyperlipidemia | 179 (63%) | 84 (59%) | 95 (67%) |
| Hypertension | 174 (61%) | 89 (63%) | 85 (60%) |
| History of colitis | 20 (7.1%) | 9 (6.3%) | 11 (7.8%) |
| History of gastroesophageal reflux disease | 94 (33%) | 46 (32%) | 48 (34%) |
| Prior pelvic surgery† | 102 (36%) | 46 (32%) | 56 (40%) |
| History of prior bowel or abdominal surgery | 54 (19%) | 29 (20%) | 25 (18%) |
| Prior abdominal or pelvic radiation therapy | 30 (11%) | 14 (10%) | 16 (11%) |
| Received neoadjuvant chemotherapy | 124 (44%) | 65 (46%) | 59 (42%) |

The values are presented as n (%) or median (interquartile range).

*No patient had an ASA score of I. †Prior pelvic surgery included radical retropubic prostatectomy and total abdominal hysterectomy.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

for proportions of patients who received vasopressors in the operating room or in the PACU (table 4). All but five patients were extubated in the operating room (table 2). Transfusion rates were also comparable between arms (table 3).

## Postoperative Ileus

The overall postoperative ileus rate in this study was 23.3% (66 of 283), with 68% (45 of 66) of those suffering from postoperative ileus requiring nasogastric tube decompression for treatment (table 4). The incidence of postoperative ileus was 25% (36 of 142) in the goal-directed fluid therapy arm and 21% (30 of 141) in the standard arm (difference in proportions, 4.1%; 95% CI, −5.8 to 13.9; $P$ = 0.418). The arms were also similar in proportion of patients requiring nasogastric tubes (15% [22 of 142] in the goal-directed fluid therapy arm vs. 16% [23 of 141] in the standard arm;

difference in proportions, −0.8, 95% CI, −9.3 to 7.7; $P$ = 0.851). Primary postoperative ileus (postoperative ileus in the absence of a major grade 3 to 5 complication) occurred in 18% (52 of 283) of patients overall, with no statistically significant difference between treatment arms: 20% (28 of 142) in the goal-directed fluid therapy arm versus 17% (24 of 141) in the standard arm (difference in proportions, 2.7%; 95% CI, −6.3 to 11.7; $P$ = 0.558).

## Other Complications

Overall, 92% (261 of 283) of patients experienced at least one complication (grades 1 to 5) within 30 days of surgery; the goal-directed fluid therapy arm had a higher rate than the standard arm (96% [136 of 142] vs. 89% [125 of 141]; difference in proportions, 5.7%; 95% CI, −0.8 to 12.2; $P$ = 0.085; table 4). However, only 15% (43 of 283) of all patients experienced a high-grade (grade 3 to 5)

**Table 2.** Intraoperative Management

| Characteristics | Both Arms Combined (N = 283) | Goal-directed Fluid Therapy (N = 142) | Standard Fluid Therapy (N = 141) | P Value |
|---|---|---|---|---|
| Type of diversion | | | | 0.306 |
| Ileal conduit | 180 (64%) | 85 (60%) | 95 (67%) | |
| Neobladder | 99 (35%) | 54 (38%) | 45 (32%) | |
| Continent stomal diversion | 4 (1.4%) | 3 (2.1%) | 1 (0.7%) | |
| Ureteral stents used | | | | 0.031 |
| None | 76 (27%) | 46 (32%) | 30 (21%) | |
| One side | 15 (5.3%) | 4 (2.8%) | 11 (7.8%) | |
| Both sides | 192 (68%) | 92 (65%) | 100 (71%) | |
| Size of bowel anastomotic stapler | | | | 0.084 |
| 60 mm | 144 (51%) | 65 (46%) | 79 (56%) | |
| 80 mm | 139 (49%) | 77 (54%) | 62 (44%) | |
| Length of surgery, min | 314.0 (275.0–355.0) | 319.0 (288.0–352.0) | 310.0 (267.0–358.0) | 0.551 |
| Length of anesthesia, min | 402.0 (350.0–445.0) | 416.0 (370.0–444.0) | 391.0 (337.0–445.0) | 0.096 |
| Extubated in operating room | 278 (98%) | 140 (99%) | 138 (98%) | 0.646 |
| Extubated in recovery room | 5 (1.8%) | 2 (1.4%) | 3 (2.1%) | |
| Type of anesthesia (general, epidural, combined) | | | | |
| General | 283 (100%) | 142 (100%) | 141 (100%) | |
| Epidural for postoperative pain control (N = 282) | | | | 0.700 |
| No | 57 (20%) | 30 (21%) | 27 (19%) | |
| Yes | 225 (80%) | 112 (79%) | 113 (81%) | |

The values are presented as n (%) or median (interquartile range).

complication within 30 days of surgery: 20 of 142 (14%) in the goal–directed fluid therapy arm *vs.* 23 of 141 (16%) in the standard arm (difference in proportions, −2.2%; 95% CI, −10.6 to 6.1; $P = 0.602$). The proportions of patients with specific complications were similar between the two arms (table 4). In addition, 50% (141 of 283) of patients suffered a complication within 30 days after their hospital discharge, 39% (109 of 283) of patients required a visit to urgent care, and 25% (70 of 283) required readmission. The 30-day perioperative mortality rate was 0.7% (2 of 283).

Acute kidney injury was more frequent in the goal–directed fluid therapy arm (56% [80 of 142] *vs.* 40% [56 of 141] in the standard arm; difference in proportions, 16.6%; 95% CI, 5.1 to 28.1; $P = 0.005$; $P = 0.170$ after adjustment for multiple testing; table 4), but all patients recovered to their baseline renal function by the time of hospital discharge as reflected by serum creatinine and glomerular filtration rate; no patient required dialysis. The imbalance in acute kidney injury incidence also accounted for the higher rate of overall genitourinary complications in the goal–directed fluid therapy arm (table 5). Overall, 34% (95 of 283) of patients had preoperative renal insufficiency defined as estimated glomerular filtration rate less than 60 ml/min, and this occurrence was similar between the two arms: 42 of 142 (30%) in the goal–directed fluid therapy group *vs.* 53 of 141 (38%) in the standard group (table 1). Unlike some of the large abdominal surgery trials, we did not find statistically significant differences between treatment arms in terms of wound infection (23% [32 of 142] in the goal-directed fluid therapy arm *vs.* 30% [42 of 141] in the standard arm; difference in proportions, −7.3%; 95% CI, −17.5 to 3.0;

$P = 0.165$) or intraabdominal abscess (8.5% [12 of 142] in the goal–directed fluid therapy arm *vs.* 7.8% [11 of 141] in the standard arm; difference in proportions, 1.3%; 95% CI, −7.4 to 10.0; $P = 0.842$; table 4). In exploratory analyses, the primary endpoint, postoperative ileus incidence, was evaluated in relation to single preoperative comorbidities but no statistically significant association was found (table 6).

The length of stay was similar between the two treatment arms: median (interquartile range), 7 (6 to 9) days in the goal–directed fluid therapy arm *versus* 7 (6 to 10) days in the standard arm (ratio of means, 0.99; 95% CI, 0.91 to 1.08; $P = 0.551$; table 4). The incidence of urgent care visits was not statistically significantly different between the two arms (42% [59 of 142] for goal–directed fluid therapy *vs.* 35% [50 of 141] for standard fluid therapy; difference in proportions, 6.1%; 95% CI, −5.2 to 17.4; $P = 0.293$).

## Discussion

This prospective randomized trial failed to demonstrate an advantage in using goal-directed fluid therapy to prevent postoperative ileus in patients undergoing radical cystectomy on an enhanced recovery pathway. Postoperative ileus is one of the most common postoperative complications after radical cystectomy: reported incidence was 2 to 32% in a recent collaborative review of radical cystectomy series, including the Memorial Sloan Kettering experience.[3] The incidence of postoperative ileus and other complications can be affected by the patient population and their comorbidities, time period examined, definitions utilized, method and quality of data collection, and use of perioperative

**Table 3.** Administered Fluid Volume, Postoperative Weight Change, and Blood Loss

| Results | Both Arms Combined (N = 283) | Goal-directed Fluid Therapy (N = 142) | Standard Fluid Therapy (N = 141) | P Value |
|---|---|---|---|---|
| Fluid volumes | | | | |
|   Protocol crystalloid, ml | 4,019 (2,890–5,730) | 2,892 (2,340–3,450) | 5,580 (4,650–6,730) | **< 0.0001** |
|   Protocol colloid (albumin 5%, packed red blood cells, FFP, and platelets), ml | 1,000 (750–1,500) | 1,000 (750–1,500) | 975 (500–1,350) | 0.053 |
|   Operating room crystalloid, ml | 2,900 (1,750–4,900) | 1,800 (1,400–2,220) | 4,850 (3,800–5,900) | **< 0.0001** |
|   Operating room colloid (albumin 5%, packed red blood cells, FFP, and platelets), ml | 800 (500–1,250) | 1,000 (750–1,250) | 750 (500–1,000) | **0.005** |
|   PACU crystalloid, ml | 840 (700–1,090) | 1,018 (791–1,370) | 750 (650–875) | **< 0.0001** |
|   PACU colloid (albumin 5%, packed red blood cells, FFP and platelets), ml | 0 (0–250) | 0 (0–250) | 0 (0–250) | 0.823 |
|   Total fluid intake during hospitalization, ml | 12,768 (9,658–17,224) | 12,657 (9,912–17,280) | 13,072 (9,363–17,157) | 0.736 |
|   Total fluid output during hospitalization, ml | 14,045 (10,875–20,335) | 13,380 (10,405–19,093) | 15,445 (11,920–21,015) | **0.044** |
|   Net fluid during hospitalization, ml | −1,689 (−4,027 to 693) | −1,296 (−3,146 to 933) | −1,986 (−5,337 to 605) | **0.020** |
|   Number of patients with negative fluid balance | 191 (67%) | 93 (65%) | 98 (70%) | 0.472 |
| Weight | | | | |
|   Peak weight during hospitalization, kg | 86.1 (76.0–98.3) | 86.2 (74.0–98.6) | 86.1 (77.0–96.9) | 0.759 |
|   Maximum weight change, kg | 2.9 (1.4–4.7) | 2.7 (1.0–4.5) | 3.0 (1.7–4.8) | 0.103 |
| Transfusion management | | | | |
|   Total estimated blood loss, ml | 700 (480–1,000) | 600 (400–900) | 750 (500–1,000) | 0.020 |
|   Number of patients with estimated blood loss of more than 1 l | 57 (20%) | 26 (18%) | 31 (22%) | 0.441 |
|   Number of patients transfused packed red blood cells in operating room | 43 (15%) | 18 (13%) | 25 (18%) | 0.236 |
|   Number of patients transfused packed red blood cells in recovery room | 70 (25%) | 31 (22%) | 39 (28%) | 0.256 |
|   Number of patients transfused packed red blood cells on the floor | 90 (32%) | 47 (33%) | 43 (30%) | 0.638 |
|   Number of patients transfused packed red blood cells during hospitalization | 142 (50%) | 69 (49%) | 73 (52%) | 0.593 |
|   Number of patients transfused more than 4 units of packed red blood cells during hospitalization | 10 (3.5%) | 3 (2.1%) | 7 (5.0%) | 0.194 |
|   Number of patients transfused FFP during hospitalization | 12 (4.2%) | 4 (2.8%) | 8 (5.7%) | 0.233 |
|   Number of patients transfused platelets during hospitalization | 10 (3.5%) | 4 (2.8%) | 6 (4.3%) | 0.512 |

The values are presented as n (%) or median (interquartile range). Colloids are defined as albumin 5% + transfusion volume. Fluids reflect the crystalloids + colloids.
Bold indicates statistically significant *P* values.
FFP, fresh frozen plasma; PACU, postanesthesia care unit.

pathways.[2,18] We designed this study based on our institution's retrospective data for postoperative ileus after radical cystectomy that demonstrated rates ranging from 25 to 32% between 2000 and 2015. In this protocol, as in all recent radical cystectomy protocols at Memorial Sloan Kettering, we used standardized definitions of complications and a prospective data capture methodology as previously described.[5,19] In this study, individual risk factors for postoperative ileus were captured and analyzed, but no differences were observed between the goal-directed and standard fluid therapy arms, as shown in table 1.

Our study is a single-population randomized goal-directed fluid therapy trial evaluating perioperative outcomes in patients undergoing radical cystectomy for bladder cancer with a new three-part algorithm designed to optimize fluid status (Supplemental Digital Content 1–3, http://links.lww.com/ALN/C391). Using SV before induction of anesthesia to establish normovolemia, minimizing SV variation intraoperatively to maintain normovolemia, and optimizing SV again once the patient reaches recovery ensure a more comprehensive approach to obtain a normovolemic status in the whole perioperative period.

In contrast to other radical cystectomy studies, such as the study by Pillai *et al.*[12] reporting on 66 patients using Doppler-optimized intraoperative fluid management and the study by Wuethrich *et al.*[20] of 166 patients using restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy, we did not find that goal-directed fluid therapy was associated with any improvement in perioperative postoperative ileus, length of stay, or other perioperative/postoperative outcomes. When it comes to secondary outcomes, our findings are more in line with a fairly recent randomized trial in colorectal surgery that showed no difference in perioperative outcomes

**Table 4.** Primary and Secondary Outcomes

| Results | Goal-directed Fluid Therapy (N = 142) | Standard Fluid Therapy (N = 141) | P Value* | Effect Size (95% CI)† |
|---|---|---|---|---|
| Protocol-defined primary outcome | | | | |
|   Postoperative ileus, either primary or secondary | 36 (25%) | 30 (21%) | 0.418 | 4.1% (−5.8 to 13.9) |
| Secondary outcomes | | | | |
|   Primary postoperative ileus (absence of other ≥Grade 3 complications) | 28 (20%) | 24 (17%) | 0.558 | 2.7% (−6.3 to 11.7) |
|   Required nasogastric tube replacement during hospitalization or prolonged use postop | 22 (15%) | 23 (16%) | 0.851 | −0.8% (−9.3 to 7.7) |
|   Total fluid intake during hospitalization, ml | 12,657 (9,912–17,280) | 13,072 (9,363–17,157) | 0.736 | Ratio: 0.99 (0.89 to 1.12) |
|   Number of patients transfused packed red blood cells during hospitalization | 69 (49%) | 73 (52%) | 0.593 | −3.2% (−14.8 to 8.5) |
|   Dose of vasopressors given intraoperatively | | | | |
|     Ephedrine dose, mg | 5 (0–20) | 5 (0–20) | 0.813 | Ratio: 0.96 (0.67 to 1.37) |
|     Phenylephrine dose, μg | 80 (0–200) | 100 (0–240) | 0.284 | Ratio: 0.68 (0.35 to 1.33) |
|   Number of patients who received vasopressors in operating room | | | | |
|     Ephedrine | 82 (58%) | 84 (60%) | 0.755 | −1.8% (−13.3 to 9.6) |
|     Phenylephrine | 79 (56%) | 88 (62%) | 0.246 | −6.8% (−18.2 to 4.7) |
|   Number of patients who received vasopressors in PACU | 4 (2.8%) | 7 (5.0%) | 0.350 | −2.1% (−6.6 to 2.4) |
|   Any complications within 30 days of surgery | 136 (96%) | 125 (89%) | 0.085‡ | 5.7% (−0.8 to 12.2) |
|     High-grade (grades 3 to 5) complication | 20 (14%) | 23 (16%) | 0.602 | −2.2% (−10.6 to 6.1) |
|     Complications postdischarge (at 30-day follow-up) | 72 (51%) | 69 (49%) | 0.766 | 1.8% (−9.9 to 13.4) |
|   Symptomatic postoperative arrhythmia | 10 (7.0%) | 10 (7.1%) | 0.987 | −0.05% (−6.0 to 5.9) |
|   Postoperative congestive heart failure | 1 (0.7%) | 2 (1.4%) | 0.557 | −0.7% (−3.1 to 1.7) |
|   Postoperative pulmonary issue (atelectasis, pneumonia, or hypoxia) | 28 (20%) | 33 (23%) | 0.451 | −3.7% (−13.2 to 5.9) |
|   Postoperative pulmonary embolus | 4 (2.8%) | 9 (6.4%) | 0.283 | −3.6% (−8.4 to 1.3) |
|   Postoperative deep vein thrombosis | 4 (2.8%) | 5 (3.5%) | 0.727 | −0.07% (−4.8 to 3.4) |
|   Postoperative acute kidney injury | 80 (56%) | 56 (40%) | 0.005§ | 16.6% (5.1 to 28.1) |
|   Discharge creatinine, mg/dl | 0.9 (0.8–1.1) | 0.9 (0.7–1.1) | 0.371 | Ratio: 1.04 (0.98 to 1.09) |
|   Discharge estimated glomerular filtration rate (Modification of Diet in Renal Disease formula), ml/min | 80 (64–95) | 81 (62–98) | 0.809 | Ratio: 1.09 (0.96 to 1.24) |
|   Urinary obstruction | 4 (2.8%) | 6 (4.3%) | 0.512 | −1.4% (−5.7 to 2.9) |
|   Urinary leak | 8 (5.6%) | 6 (4.3%) | 0.593 | 1.4% (−3.7 to 6.4) |
|   Symptomatic postoperative urinary tract infection | 25 (18%) | 23 (16%) | 0.772 | 1.3% (−7.4 to 10.3) |
|   Intraabdominal abscess | 12 (8.5%) | 11 (7.8%) | 0.842 | 1.3 (−7.4 to 10.0) |
|   Sepsis | 14 (10%) | 14 (10%) | 0.984 | −0.07% (−7.0 to 6.9) |
|   Wound infection | 32 (23%) | 42 (30%) | 0.165 | −7.3 (−17.5 to 3.0) |
|   Wound dehiscence | 3 (2.1%) | 5 (3.5%) | 0.467 | −1.4% (−5.3 to 2.4) |
|   Length of stay in hospital, days | 7 (6–9) | 7 (6–10) | 0.551 | Ratio: 0.99 (0.91 to 1.08) |
|   Required urgent care center visit within 30 days of surgery | 59 (42%) | 50 (35%) | 0.293 | 6.1% (−5.2 to 17.4) |
|   Required readmit to hospital within 30 days | 35 (25%) | 35 (25%) | 0.973 | 0.2% (−10.2 to 9.9) |
|   Required return to operating room as inpatient | 6 (4.2%) | 2 (1.4%) | 0.154 | 2.8% (−1.0 to 6.6) |
|   Required operating room procedure within 30 days as outpatient or during readmission to Memorial Sloan Kettering | 0 (0%) | 3 (2.1%) | 0.081 | −2.1% (−4.5 to 0.3) |
|   Required interventional radiology procedure during primary hospitalization | 6 (4.2%) | 7 (5.0%) | 0.766 | −0.7% (−5.6 to 4.1) |
|     Required outpatient interventional radiology procedure within 30 days of surgery | 10 (7.0%) | 11 (7.8%) | 0.808 | −0.8% (−6.9 to 5.3) |

The values are presented as n (%) or median (interquartile range).

*The *P* values (before multiple-testing adjustments) were calculated using the chi-square test for categorical outcomes and the Wilcoxon rank sum test for continuous outcomes. †Effect sizes were based on difference in proportions for binary outcomes and ratio of means for continuous outcomes. The width of 95% CI have not been adjusted for multiple testing. ‡After adjustment for multiple testing, the *P* value = 0.938 for any complications within 30 days of surgery. §After adjustment for multiple testing, the *P* value = 0.170 for acute kidney injury.

PACU, postanesthesia care unit.

with goal–directed fluid therapy.[15] Unlike the FEDORA trial,[9] which is a more recent study comparing the use of goal–directed hemodynamic therapy to predefined standard care and which showed an outcome benefit for the use of goal–directed therapy, our results did not confirm a benefit and actually showed an increased risk of acute kidney injury with goal–directed therapy. This dissimilarity could be attributed to the different algorithm used in the FEDORA trial, with a more comprehensive hemodynamic approach to optimization using inotropic and pressure support driven by the algorithm.[9] Another recent study, RELIEF (Restrictive *vs.* Liberal Fluid), reported by Myles *et al.*,[11] compared the use of liberal *versus* restricted fluid management in major abdominal surgery and found no difference in disability-free survival at 1 yr but found an increased rate of acute kidney injury in the restrictive arm. Our study's algorithm more closely resembled the algorithm in the RELIEF trial,[11] with additional fluid in the restrictive arm

**Table 5.** Frequency of 30-day Postoperative Complications by Category

| Complication Category | Overall (N = 283) | Goal-directed Fluid Therapy (N = 142) | Standard Fluid Therapy (N = 141) | P Value |
|---|---|---|---|---|
| Surgical | 11 (3.9%) | 4 (2.8%) | 7 (5.0%) | 0.350 |
| Wound | 104 (37%) | 46 (32%) | 58 (41%) | 0.127 |
| Pulmonary | 56 (20%) | 27 (19%) | 29 (21%) | 0.743 |
| Neurologic | 64 (23%) | 39 (27%) | 25 (18%) | 0.050 |
| Genitourinary | 144 (51%) | 84 (59%) | 60 (43%) | **0.005** |
| Infection | 76 (27%) | 39 (27%) | 37 (26%) | 0.816 |
| Gastrointestinal | 103 (36%) | 55 (39%) | 48 (34%) | 0.412 |
| Cardiac | 61 (22%) | 31 (22%) | 30 (21%) | 0.910 |
| Bleeding | 106 (37%) | 54 (38%) | 52 (37%) | 0.842 |
| Miscellaneous | 29 (10%) | 14 (10%) | 15 (11%) | 0.829 |
| Thromboembolic | 20 (7.1%) | 7 (4.9%) | 13 (9.2%) | 0.159 |

The patients were recorded more than once if they had more than one complication within a category. Please refer to Shabsigh et al.[5] for specific complications in each category. Bold indicates statistically significant P values.

**Table 6.** Relationship of Preoperative Comorbidities to Postoperative Ileus

| Characteristics | Postoperative Ileus (N = 66; 23%) | No Postoperative Ileus (N = 217; 77%) | P Value |
|---|---|---|---|
| History of COPD (emphysema, asthma, chronic bronchitis) | 12 (18%) | 34 (16%) | 0.628 |
| History of coronary artery disease | 9 (14%) | 49 (23%) | 0.115 |
| Myocardial infarction in past | 3 (4.5%) | 13 (6.0%) | 0.656 |
| Longstanding arrhythmia | 3 (4.5%) | 6 (2.8%) | 0.470 |
| Prior venous embolic event (deep vein thrombosis, pulmonary embolism) | 8 (12%) | 28 (13%) | 0.867 |
| Diabetes | | | |
| Non–insulin-dependent diabetes | 10 (15%) | 39 (18%) | 0.596 |
| Insulin-dependent diabetes | 3 (4.5%) | 9 (4.1%) | 0.888 |
| Peripheral neuropathy | | | 0.796 |
| None | 54 (82%) | 182 (84%) | |
| Diabetes-related neuropathy | 1 (1.5%) | 5 (2.3%) | |
| Non-diabetes-related neuropathy | 11 (17%) | 30 (14%) | |
| Hyperlipidemia | 43 (65%) | 136 (63%) | 0.715 |
| Hypertension | 39 (59%) | 135 (62%) | 0.648 |
| History of colitis | 3 (4.5%) | 17 (7.8%) | 0.361 |
| History of gastroesophageal reflux disease | 20 (30%) | 74 (34%) | 0.566 |
| Prior pelvic surgery* | 21 (32%) | 81 (37%) | 0.414 |
| History of prior bowel or abdominal surgery | 11 (17%) | 43 (20%) | 0.569 |
| Prior abdominal or pelvic radiation therapy | 10 (15%) | 20 (9.2%) | 0.170 |
| Charlson Comorbidity Index | 1 (0–2) | 1 (0–2) | 0.848 |

The values are presented as n (%) or median (interquartile range).
*Prior pelvic surgery included radical retropubic prostatectomy and total abdominal hysterectomy.
COPD, chronic obstructive pulmonary disease.

driven by cardiac output monitoring, than the FEDORA[9] algorithm. This could explain the similarity of our results to RELIEF and the dissimilarity with FEDORA. Moreover, the RELIEF liberal arm had a fluid administration very similar to our standard arm; in both our data and RELIEF, there was no harm in the more liberal fluid administration; this might suggest that the initial teaching of fluid restriction in Enhanced Recovery After Surgery pathways might not be beneficial.[11]

Differences in postoperative ileus and perioperative outcomes between studies may also be partly explained by variations between studies in definitions, data capture, postoperative enhanced recovery pathways, time of follow-up, and patient comorbidities.[18] For instance, the study by Wuethrich et al.[13] never clearly defined what they considered postoperative ileus and had a relatively high 22% rate of "constipation" (also not defined) in the control arm. The study by Pillai et al.[12] defined ileus by the subjective measures "absence of bowel sound with a painful abdomen," with no delineation of parameters regarding time to tolerance of oral intake, radiographic results, or intervention (i.e., nasogastric tube use), which may have led to an underestimated ileus rate. We

had a highly comorbid population (table 1), with 70% of our population having an American Society of Anesthesiologists score of III to IV, the overall population having an age-adjusted Charlson Comorbidity Index 4 or higher, and few medical restrictions to study entry (only active atrial fibrillation or body mass index of more than 45 kg/m$^2$ because of the limitations of SV variation reading). Despite this, there were no statistically significant differences in high-grade complications (15% overall) or categories of complications between treatment groups. There was a higher incidence of transient acute kidney injury in the goal-directed fluid therapy group (56% *vs.* 40%; multiple testing adjusted $P = 0.170$).

As in the recent goal-directed fluid therapy study reported by Gómez-Izquierdo et al.,[15] we also showed a statistically significant difference in intraoperative fluid administration, but when comparing the total fluid administration during the hospital stay, the difference disappears even more dramatically in our population, raising the question of whether perioperative fluid administration is too small of a proportion compared with the full hospital stay to make a considerable outcome difference. This would strengthen the theory that the success in postoperative enhanced recovery pathways lies in multiple changes and not a solitary intervention.

A more in-depth analysis of the overall population regardless of treatment arm showed no association between any of the preoperative comorbidities and the occurrence of postoperative ileus (table 6). This would confirm that no prior condition or surgery predisposes any patient to developing postoperative ileus, and as such we cannot establish any early interventions for high-risk patients based on preoperative comorbidities.

There are several limitations in this study. This is a single-center trial with a very homogeneous population and a single surgery; however, this actually reduces variability in algorithm execution, allowing us to draw more precise conclusions regarding fluid administration and its effects. The algorithm used intraoperatively was based on SV variation minimization. More recent studies have used SV optimization even during the intraoperative phase; however, our thought was that SV variation was easier to implement in the operating room and that compliance to the execution of the algorithm would be higher. Moreover, the preinduction optimization based on a passive leg raise and fluid optimization might seem time-consuming, but considering the average length of this procedure, we believe that the additional time could be offset by performing the optimization during room set-up, decreasing the impact on overall operating room utilization. Another limitation, if trying to apply this technique to different abdominal surgeries, can be the relatively long PACU stay, but we believe this technique is better designed for more complex surgeries that require longer postoperative observation to begin with. A third limitation was that the control arm was designed with a fixed algorithm, but we believed that creating an algorithm for the standard arm would minimize the variability in fluid administration still found in different practitioners, allowing us to draw more specific conclusions with a smaller population.

Finally, the two arms received different types of fluids; we designed our protocol similarly to the one used by Ramsingh et al.[8] and decided to maintain the volume expansion with albumin 5% for both arms, one guided by cardiac output monitoring and the other guided by blood loss. The study by Pearse et al. (commonly known as OPTIMISE trial) that was published in 2014 used a similar approach.[10] The more recent study by Kabon et al.[21] looked specifically at the effect of colloid *versus* crystalloid in a goal-directed fluid therapy setting and found no difference in either complications or toxicity, which confirms the safety of this approach.

In conclusion, we did not find that individualized goal-directed fluid therapy had a benefit for radical cystectomy patients; therefore, this method has not been adopted as a standard of care at our institution. Fluid management is now based on standard monitoring, with the adoption of advanced hemodynamic monitoring in cases with excessive blood loss or patients with multiple comorbidities.

## Research Support

## Competing Interests

Dr. Fischer has undertaken paid consulting work for Edwards Lifesciences (Irvine, California). The other authors declare no competing interests.

## Reproducible Science

Full protocol available at: arslancv@mskcc.org. Raw data available at: arslancv@mskcc.org.

## Correspondence

Address correspondence to Dr. Arslan-Carlon: Memorial Sloan Kettering Cancer Center, 1275 York Avenue, C336, New York, New York 10065. arslancv@mskcc.org. ANESTHESIOLOGY's articles are made freely accessible to all readers on www.anesthesiology.org, for personal use only, 6 months from the cover date of the issue.

## References

1. Giglio MT, Marucci M, Testini M, Brienza N: Goal-directed haemodynamic therapy and gastrointestinal complications in major surgery: A meta-analysis of randomized controlled trials. Br J Anaesth 2009; 103:637–46

2. Vather R, Trivedi S, Bissett I: Defining postoperative ileus: Results of a systematic review and global survey. J Gastrointest Surg 2013; 17:962–72

3. Froehner M, Brausi MA, Herr HW, Muto G, Studer UE: Complications following radical cystectomy for bladder cancer in the elderly. Eur Urol 2009; 56:443–54

4. Svatek RS, Fisher MB, Williams MB, Matin SF, Kamat AM, Grossman HB, Nogueras-González GM, Urbauer DL, Dinney CP: Age and body mass index are independent risk factors for the development of postoperative paralytic ileus after radical cystectomy. Urology 2010; 76:1419–24

5. Shabsigh A, Korets R, Vora KC, Brooks CM, Cronin AM, Savage C, Raj G, Bochner BH, Dalbagni G, Herr HW, Donat SM: Defining early morbidity of radical cystectomy for patients with bladder cancer using a standardized reporting methodology. Eur Urol 2009; 55:164–74

6. Gan TJ, Soppitt A, Maroof M, el-Moalem H, Robertson KM, Moretti E, Dwane P, Glass PS: Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. Anesthesiology 2002; 97:820–6

7. Cannesson M, Ramsingh D, Rinehart J, Demirjian A, Vu T, Vakharia S, Imagawa D, Yu Z, Greenfield S, Kain Z: Perioperative goal-directed therapy and postoperative outcomes in patients undergoing high–risk abdominal surgery: A historical-prospective, comparative effectiveness study. Crit Care 2015; 19:261

8. Ramsingh DS, Sanghvi C, Gamboa J, Cannesson M, Applegate RL 2nd: Outcome impact of goal directed fluid therapy during high risk abdominal surgery in low to moderate risk patients: A randomized controlled trial. J Clin Monit Comput 2013; 27:249–57

9. Calvo-Vecino JM, Ripollés-Melchor J, Mythen MG, Casans-Francés R, Balik A, Artacho JP, Martínez-Hurtado E, Serrano Romero A, Fernández Pérez C, Asuero de Lis S; FEDORA Trial Investigators Group: Effect of goal-directed haemodynamic therapy on postoperative complications in low–moderate risk surgical patients: A multicentre randomised controlled trial (FEDORA trial). Br J Anaesth 2018; 120:734–44

10. Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blunt M, Ackland G, Grocott MP, Ahern A, Griggs K, Scott R, Hinds C, Rowan K; OPTIMISE Study Group: Effect of a perioperative, cardiac output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: A randomized clinical trial and systematic review. JAMA 2014; 311:2181–90

11. Myles PS, Bellomo R, Corcoran T, Forbes A, Peyton P, Story D, Christophi C, Leslie K, McGuinness S, Parke R, Serpell J, Chan MTV, Painter T, McCluskey S, Minto G, Wallace S; Australian and New Zealand College of Anaesthetists Clinical Trials Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Restrictive *versus* liberal fluid therapy for major abdominal surgery. N Engl J Med 2018; 378:2263–74

12. Pillai P, McEleavy I, Gaughan M, Snowden C, Nesbitt I, Durkan G, Johnson M, Cosgrove J, Thorpe A: A double-blind randomized controlled clinical trial to assess the effect of Doppler optimized intraoperative fluid management on outcome following radical cystectomy. J Urol 2011; 186:2201–6

13. Wuethrich PY, Burkhard FC, Thalmann GN, Stueber F, Studer UE: Restrictive deferred hydration combined with preemptive norepinephrine infusion during radical cystectomy reduces postoperative complications and hospitalization time: A randomized clinical trial. Anesthesiology 2014; 120:365–77

14. Clavien PA, Sanabria JR, Strasberg SM: Proposed classification of complications of surgery with examples of utility in cholecystectomy. Surgery 1992; 111:518–26

15. Gómez-Izquierdo JC, Trainito A, Mirzakandov D, Stein BL, Liberman S, Charlebois P, Pecorelli N, Feldman LS, Carli F, Baldini G: Goal-directed fluid therapy does not reduce primary postoperative ileus after elective laparoscopic colorectal surgery: A randomized controlled trial. Anesthesiology 2017; 127:36–49

16. American Kidney Fund. Stages of chronic kidney disease (CKD). Available at: https://www.kidneyfund.org/kidney-disease/chronic-kidney-disease-ckd/stages-of-chronic-kidney-disease/. Accessed on November 21, 2019.

17. Winer AG, Sfakianos JP, Puttanniah VG, Bochner BH: Comparison of perioperative outcomes for epidural *versus* intravenous patient-controlled analgesia after radical cystectomy. Reg Anesth Pain Med 2015; 40:239–44

18. Donat SM: Standards for surgical complication reporting in urologic oncology: Time for a change. Urology 2007; 69:221–5

19. Cannesson M, Musard H, Desebbe O, Boucau C, Simon R, Hénaine R, Lehot JJ: The ability of stroke volume variations obtained with Vigileo/FloTrac system to monitor fluid responsiveness in mechanically ventilated patients. Anesth Analg 2009; 108:513–7

20. Wuethrich PY, Burkhard FC: Improved perioperative outcome with norepinephrine and a restrictive fluid administration during open radical cystectomy and urinary diversion. Urol Oncol 2015; 33:66.e21–4

21. Kabon B, Sessler DI, Kurz A; Crystalloid–Colloid Study Team: Effect of intraoperative goal-directed balanced crystalloid *versus* colloid administration on major postoperative morbidity: A randomized trial. Anesthesiology 2019; 130:728–44