GYNECOLOGY

# Validation of an enhanced recovery after surgery protocol in gynecologic surgery: an Italian randomized study

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**BACKGROUND:** The enhanced recovery after surgery concept, which was introduced 20 years ago, is based on a multimodal approach to improve the functional rehabilitation of patients after surgery.

**OBJECTIVE:** This study aimed to validate an enhanced recovery after surgery protocol in gynecologic surgery for both benign and malignant diseases (endometrial cancer and advanced ovarian cancer) and to measure the adherence to the enhanced recovery after surgery protocol items in a randomized trial setting.

**STUDY DESIGN:** In this trial (NCT03347409), we randomly assigned patients to undergo standard perioperative care or enhanced recovery after surgery protocol. The primary outcome is a shorter length of stay in favor of the enhanced recovery after surgery protocol. Secondary outcomes include measurement of adherence to the enhanced recovery after surgery protocol items: comparison of postoperative pain, vomiting, and nausea; anesthesiologic and surgical complications up to 30 days after surgery; rate of readmissions; the time to event in hours for bowel movements, flatus, drinking, hunger, eating, and walking; and the quality of recovery using a validated questionnaire (QoR-15). Finally, we explored the length of stay in the prespecified subgroups at randomization, based on the type of surgical access and gynecologic disease.

**RESULTS:** A total of 168 women were available for analysis: 85 women (50.6%) were assigned to the standard perioperative care group, and 83

women (49.4%) were assigned to the enhanced recovery after surgery protocol group. The 2 groups were similar for age, body mass index, comorbidities, anesthesiological risk, smoking habits, surgical access, and complexity of surgical procedures. Seventy-two patients (42.9%) underwent surgery for benign disease, 48 (28.6%) for endometrial cancer, and 48 (28.6%) for ovarian cancer. Women in the enhanced recovery after surgery protocol group had a shorter length of stay (median: 2 [interquartile range, 2—3] vs 4 [interquartile range, 4—7] days; $P<.001$). A decreased rate of postoperative complications was noted for the enhanced recovery after surgery protocol group, as well as an earlier time to occur for all the events. Mean adherence to protocol items was 84.8% (95% confidence interval, 79.7—89.8), and we registered a better satisfaction in the enhanced recovery after surgery protocol group. The shortening of the length of stay was confirmed also in the prespecified subgroup analysis.

**CONCLUSION:** Application of the enhanced recovery after surgery protocol in gynecologic surgery translated to a shorter length of stay regardless of surgical access and type of gynecologic disease. Adherence to the enhanced recovery after surgery protocol items in the setting of a randomized trial was high.

**Key words:** enhanced recovery after surgery, gynecologic surgery, gynecology, ovarian cancer

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The enhanced recovery after surgery (ERAS) concept was introduced 20 years ago, and it is based on a multimodal approach to improve the functional rehabilitation of patients after surgery.[1] ERAS has demonstrated a reduction in the length of stay (LOS) without increasing complication or readmission rates.[2] The ERAS protocols include several items, including a preoperative counseling; a standardized approach in anesthetic management and

## EDITORS' CHOICE

in postoperative strategies to prevent nausea, vomiting, and pain; a restriction of tubes and catheters; early mobilization; and oral feeding.[2,3]

Most of the experiences and outcomes with ERAS protocols were published in patients undergoing colorectal surgery,[4] but moderate pieces of evidence were reported also in gynecologic surgery.[5] Minimally invasive surgery is a widely used technique in gynecology[6,7] and is an important component of ERAS in many specialties, demonstrating a synergistic effect in optimizing outcomes after surgery.[8] Nevertheless, the traditional open surgery approach still plays a relevant role in gynecology, particularly for advanced malignant disease.[9,10] Systematic application of ERAS protocol is difficult and cumbersome,

because of the consolidated personal conviction of healthcare staff, resulting in slow implementation rates.[11,12] Furthermore, only a few prospective randomized trials have been conducted so far specifically addressing the impact of ERAS in gynecologic surgery.[13,14] In addition, the difficulty in accomplishing necessary compliance to all protocol items calls for new implementation strategies.[3,15,16]

In this study, we aimed to validate the contribution of an ERAS protocol in gynecologic surgery for both benign and oncological diseases in a randomized trial setting and to measure the adherence to the ERAS protocol items.

## Methods

We conducted a prospective randomized trial enrolling women who underwent major gynecologic surgery during the study period from December 2017 to

July 2019 at Azienda Socio Sanitaria Territoriale of Spedali Civili of Brescia, a tertiary university hospital in northeastern Italy. We randomly assigned patients to undergo standard perioperative care (SPC) or ERAS protocol. We obtained approval by the local institutional review board (NP2722) and written informed consent before enrollment. The study was registered at ClinicalTrials.gov (NCT03347409). Women were eligible for enrollment if their age was ≥18 years and ≤75 years and they were a candidate for major gynecologic surgery for benign disease (including leiomyomas, endometriosis, and functional pathology of the uterus[17]) or malignant disease (including endometrial cancer or advanced-stage ovarian cancer) that contemplates at least total hysterectomy with either an endoscopic or an open approach. We excluded patients with American Society of Anesthesiologists (ASA) risk ≥4 or with planned discharge from the intensive care unit, Karnofsky performance status <70, contraindication to locoregional anesthesia (ie, coagulative disorders), organ failure or severe dysfunction, history of previous or current alcohol or drug abuse, a comorbidity-polypharmacy score[18] ≥22, and presence of a psychiatric condition or language barrier. Furthermore, we excluded patients affected by cervical cancer given the early findings of the Laparoscopic Approach to Cervical Cancer trial to avoid future unbalanced accrual regarding surgical access. Baseline characteristics of the patients included age, ethnicity, body mass index, ASA, risk of postoperative nausea and vomiting (PONV) using the Apfel score,[19] and values of the Malnutrition Universal Screening Tool,[20] a tool that classifies nutritional status in a 3-level scale (ranging from low to high risk of malnutrition). We collected anesthesiological data such as preanesthetic medications, type of anesthesia adopted, pharmacologic approach to prevent and treat PONV, goal-directed fluid therapy, maintenance of intraoperative normothermia, and postoperative pain control strategies. Surgical parameters and outcomes were collected, and they include the type of surgery (extent of surgical procedures stratified according to the type of gynecologic disease, in particular for endometrial cancer[21] and ovarian cancer[22,23]), type of surgical access (endoscopic vs open surgery), duration of surgery, estimated blood loss, and placement of peritoneal drains and nasogastric tube.

The primary endpoint of the study was to demonstrate a statistically significant reduction of the LOS, measured as the number of days spent in the hospital, regardless of surgical access and type of gynecologic disease. Of note, all the surgeries started as the first case of the day at 9 AM.

The secondary endpoints of the study were to measure the LOS in each prespecified subgroup; to assess the immediate postoperative benefits in terms of reduction of PONV, pain, and postoperative ileus (POI); and to assess the rates of anesthesiological and intra- and postoperative complications up to 30 days and the rates of readmissions. We included further indicators in the analysis as the hours elapsed from the end of the surgery to the first time to hunger, tolerance to clear fluid and food, libitum diet, urination, flatus, first bowel movement, mobilization in a chair, and walk.

We investigated the satisfaction of the patients using a validated questionnaire (QoR-15)[24] that was administered 24 hours after surgery and at discharge. Finally, we assessed the rate of adherence to the various items in the ERAS protocol group. A randomized trial on ERAS is difficult to perform because running SPC and ERAS protocol simultaneously carries the risk of mixing the elements. Hence, to avoid any unintentional biases, the investigators were excluded from the clinical management of the patients. Furthermore, we split the surgical, anesthesiological, and nurse teams involved in the study, without the possibility of changes in the team's composition, and we enrolled the patients minimizing the overlapping of the hospitalization. Surgical teams were both composed of 2 senior surgeons and 2 senior fellows. Each surgery was performed by 2 senior surgeons and 1 senior fellow. The details of the ERAS protocol are available in the Supplemental Material section and a comparison with SPC was available in the Supplemental Table.

## Discharge criteria

Patients were discharged at the time the following criteria were met: pain controlled numeric rating scale (NRS) <4 with paracetamol and nonsteroidal antiinflammatory drugs taken per os, absence of fever (<37.5°C) and PONV, presence of flatus or passed feces, fluid and free diet tolerance, ability to independent mobilization, and feeling fit for discharge. These criteria were assessed every 3 hours during the day shift (7 AM to 6 PM) by ward nurses. In detail, ward nurses obtained NRS values by asking the patient to point to a number ranging

from 0 to 10 corresponding to the pain experienced at the time of the assessment where a greater value corresponds to higher pain and 0 corresponds to no pain.

## Sample size

In a sample of 55 consecutive historical patients treated with major gynecologic surgery at our department, we found a mean of 5 days of LOS with a standard deviation (SD) of 3.5, and hence, we estimated a decrease of 40% as an outcome of interest. The probability was 95% that the study will detect a difference at a 2-sided .05 significance level if the true difference between the 2 groups was at least 2 units in LOS, given an SD of 3.5 units with at least 160 patients enrolled in this 2-group parallel design study.

## Statistical analysis

We adopted a stratified permuted block randomization, and all analyses were performed on an intention-to-treat basis. We planned prespecified subgroup analyses according to the surgical access and the type of gynecologic disease, and hence, we considered them as stratum during the randomization process. We conducted protocol comparisons of continuous variables with parametric or nonparametric methods, as appropriate. We used a log-rank test to compare the LOS within groups and prespecified subgroups. We assessed the consistency of the ERAS protocol effect across each subgroup with a 2-way analysis of variance interaction test that examined, respectively, the effect of surgical access and type of gynecologic disease on normalized LOS. Simple descriptive rates were adopted to measure the adherence to ERAS protocol items.

## Results

From December 2017 to July 2019, we screened 199 women, and we finally randomized 168 participants. Of these, we excluded from analysis 2 patients in the SPC group and 6 patients in the ERAS protocol group either because they withdrew the consent before receiving the allocated treatment or because we planned the surgery for the wrong week.



### FIGURE
**Consolidated Standards of Reporting Trials flow diagram**
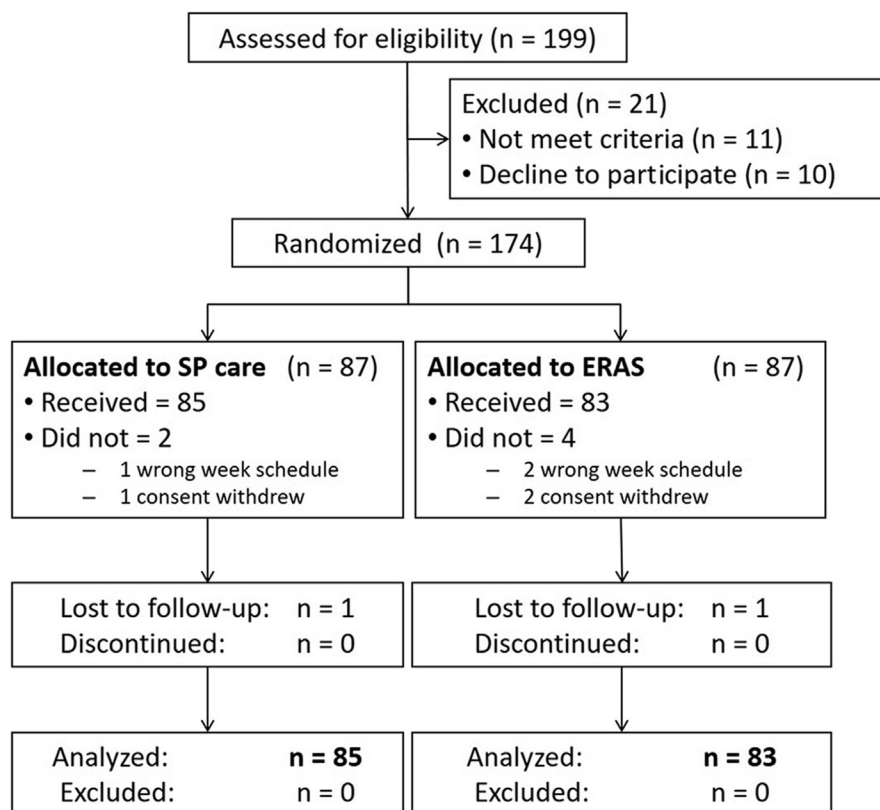
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We finally enrolled 85 (50.6%) and 83 (49.4%) women, respectively, in the SPC group and ERAS protocol group (Figure). There were no baseline differences between the 2 study groups (Table 1). As the primary outcome, we confirmed a statistically significant shortening of the LOS for the women enrolled in the ERAS protocol group (median: 2 vs 4 days; $P<.001$), as reported in Table 2. Among the secondary outcomes, we confirmed the consistency of ERAS benefits in the prespecified subgroups, as reported by the median LOS in Table 2. Of note, we found a statistically significant quantitative interaction of the study groups with the type of surgical access ($P=.019$) and gynecologic disease ($P=.011$), respectively. The ERAS protocol group was not associated with a persistent statistically significant reduction of postoperative nausea and postoperative vomiting up to 24 hours after surgery, and we confirmed

this finding after observation of PONV as a composite outcome (Supplemental Figures 1, 2, and 3). We did not find a statistically significant difference in pain control at discharge from the operating room, 3 and 6 hours later, although we found statistically significant different values of NRS at 12 and 24 hours after surgery, in favor of the ERAS protocol group (Supplemental Figure 4). In the SPC group, 74% of patients requested at least 1 dose of parenteral analgesia vs 37% in the ERAS protocol group ($P<.001$). Only 3.4% of patients in the ERAS group vs 30% in the SPC group requested more than 3 doses of parenteral analgesic ($P<.001$) and with a mean difference use of total morphine equianalgesic dose of 7.5 mg (95% confidence interval [CI], 3.6−11.5; $P<.001$). The placement of thoracic epidural analgesia (TEA) was more frequent in the ERAS protocol group (43% vs 13%; $P<.001$), although opioid-based

## TABLE 1
### Baseline characteristics of the study population

| Characteristics | All patients (n=168) | SPC (n=85) | ERAS (n=83) | P value |
|---|---|---|---|---|
| **Age** | | | | |
| Mean (range) | 55.7 (32—75) | 54.9 (32—75) | 56.5 (32—75) | .342 |
| Median (IQR) | 55 (48—65) | 55 (47—63) | 55 (48—66) | |
| **BMI** | | | | |
| Mean (range) | 25.5 (16.2—43.2) | 25.2 (16.2—43.2) | 25.6 (18.0—38.6) | .559 |
| Median (IQR) | 24.9 (21.0—28.5) | 24.2 (21—28.8) | 25.0 (21.3—28.6) | |
| **Educational status** | | | | |
| Secondary or lower | 83 (49.4) | 41 (48.2) | 42 (50.6) | .439 |
| Tertiary or higher | 85 (50.6) | 44 (51.8) | 41 (49.4) | |
| **CPS** | | | | |
| Mild (0—7) | 146 (86.9) | 73 (85.9) | 73 (88.0) | .906 |
| Moderate (8—15) | 18 (10.7) | 10 (11.8) | 12 (9.6) | |
| Severe (16—21) | 4 (2.4) | 2 (2.4) | 2 (2.4) | |
| **ASA risk** | | | | |
| 0—2 | 126 (75.0) | 62 (72.9) | 64 (77.1) | .353 |
| >3 | 42 (25.0) | 23 (27.1) | 19 (22.9) | |
| **Apfel score** | | | | |
| Low risk (1—2) | 100 (59.5) | 49 (57.6) | 51 (61.4) | .747 |
| Intermediate risk (3) | 60 (35.7) | 31 (36.5) | 29 (34.9) | |
| High risk (4) | 8 (4.6) | 5 (5.9) | 3 (3.6) | |
| Hypertension | 54 (31.0) | 30 (35.3) | 24 (29.0) | .360 |
| Diabetes | 11 (6.3) | 5 (5.9) | 6 (67.2) | .483 |
| Active smoking | 16 (9.5) | 8 (9.4) | 8 (9.6) | .584 |
| **MUST** | | | | |
| 0—1 | 172 (98.8) | 83 (98.8) | 82 (98.8) | .567 |
| 2 | 2 (1.2) | 1 (1.2) | 1 (1.2) | |
| **Gynecologic disease** | | | | |
| Benign | 72 (42.9) | 36 (42.4) | 36 (43.4) | .971 |
| Endometrial cancer | 48 (28.6) | 24 (28.2) | 24 (28.9) | |
| Ovarian cancer (advanced) | 48 (28.6) | 25 (29.4) | 24 (27.7) | |
| **Surgical access** | | | | |
| Endoscopy | 73 (43.4) | 39 (45.9) | 34 (41.0) | .796 |
| Open (Pfannenstiel) | 30 (17.9) | 15 (17.6) | 15 (18.1) | |
| Open (longitudinal) | 65 (38.7) | 31 (36.55) | 34 (41.0) | |
| **Surgical procedures** | | | | |
| BPLND | 51 (30.4) | 25 (29.4) | 26 (31.3) | .787 |
| PALND | 13 (7.7) | 6 (7.1) | 7 (8.4) | .739 |
| Omentectomy | 48 (28.6) | 25 (29.4) | 23 (27.7) | .807 |
| Bowel resection | 13 (7.8) | 7 (8.2) | 6 (7.2) | .807 |
| Diaphragm resection | 4 (2.4) | 2 (2.4) | 2 (2.4) | .981 |

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**TABLE 1**
**Baseline characteristics of the study population** (continued)

| Characteristics | All patients (n=168) | SPC (n=85) | ERAS (n=83) | Pvalue |
|---|---|---|---|---|
| Surgery duration, min | | | | |
|     Mean (range) | 149 (40—508) | 160 (61—508) | 139 (40—340) | .120 |
|     Median (IQR) | 130 (100—173) | 138 (102—195) | 127 (95—166) | |
| EBL, mL | | | | |
|     Mean (range) | 305 (15—2800) | 315 (15—1500) | 300 (15—2800) | .335 |
|     Median (IQR) | 200 (100—350) | 200 (100—400) | 200 (100—350) | |

Data are presented as number (percentage), unless otherwise specified.

*ASA,* American Society of Anesthesiologists; *BMI,* body mass index; *BPLND,* bilateral pelvic lymph nodes dissection; *CPS,* comorbidity-polypharmacy score; *EBL,* estimated blood loss; *ERAS,* enhanced recovery after surgery; *IQR,* interquartile range; *MUST,* Malnutrition Universal Screening Tool; *PALND,* paraaortic lymph nodes dissection; *SPC,* standard perioperative care.

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postoperative analgesia remained predominant in the SPC group (53.1% vs 8.2%; *P*<.001). On the contrary, intrathecal morphine was administered more frequently in the ERAS protocol group (23.1% vs 48.2%; *P*<.001).

We registered a statistically significant earlier time to occur after surgery for all the events explored (Table 3). There were no statistically significant differences between the groups when comparing anesthesiological and intraoperative complications, as well as the rates of readmission (Table 3). Conversely, we found a higher rate of postoperative complication in the SPC group (33.3% vs 18.3%; *P*=.02). We found a mean adherence rate of 84.8% (95% CI, 79.7—89.8) to ERAS protocol items, with a median of 89% (Table 4). In the pre-, intra-, and postoperative settings, mean adherence rates were 80.3% (95% CI, 64.9—95.7), 86.6% (95% CI, 78.2—94.5), and 86.3% (95% CI, 82.3—90.4), respectively. Finally, we found a greater satisfaction using QoR-15 questionnaire at 24 hours after surgery for patients in the ERAS protocol group (123.1 vs 94.0 total points; *P*<.001) and at discharge (134.2 vs 120.6 total points; *P*<.001).

## Structured Discussion
### Principal findings
The ERAS protocol resulted in a statistically significant shortening of LOS regardless of surgical access and type of gynecologic disease. We observed a

reduced incidence of postoperative complications and no differences in terms of anesthesiological and intraoperative complications and the rate of readmissions. We found a greater satisfaction among patients enrolled in the ERAS protocol group, with adherence rates in the upper end quartile.

## Results
Our results confirmed the feasibility, safety, and benefits of the ERAS protocol in major gynecologic surgery with stronger evidence than the current published literature. In fact, all the

perioperative guidelines for gynecologic surgery were inherited by colorectal experience because, to date, scanty randomized evidence is available for systematic application of ERAS in gynecology. Adequate comparisons of benefits of enhanced recovery in this setting are well described in a review by Scheib et al.[14] In this review, most studies were represented by retrospective experiences, followed by prospective studies. Randomized studies were the minority, and they were all conducted in a much more selective background, such as abdominal total hysterectomy for a

**TABLE 2**
**LOS for all patients and across prespecified subgroups**

| Group | All patients (n=168) | SPC (n=85) | ERAS (n=83) | Pvalue |
|---|---|---|---|---|
| Primary analyses of LOS | | | | |
|     Mean (range) | 4.5 (1—23) | 6.1 (3—23) | 2.8 (1—8) | <.001[a] |
|     Median (IQR) | 3 (2—5) | 4 (2—7) | 2 (2—3) | |
| LOS by diagnosis, median (IQR) | | | | |
|     Benign disease | 3 (2—4) | 4 (3—4) | 2 (1—3) | <.001[a] |
|     Endometrial cancer | 3 (2—4) | 4 (4—5) | 2 (2—3) | <.001[a] |
|     Ovarian cancer | 6 (4—8) | 7 (6—13) | 4 (3—6) | <.001[a] |
| LOS by surgical access, median (IQR) | | | | |
|     Endoscopy | 3 (2—4) | 4 (3—4) | 2 (2—2) | <.001[a] |
|     Open | 4 (3—7) | 6 (4—8) | 3 (2—4) | <.001[a] |

*ERAS,* enhanced recovery after surgery; *IQR,* interquartile range; *LOS,* length of stay; *SPC,* standard perioperative care.

[a] Statistically significant value.

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## TABLE 3
## Time to event in hours and principal outcomes

| Outcomes | All patients (n=168) | SPC (n=85) | ERAS (n=83) | Pvalue |
|---|---|---|---|---|
| Time to mobilization in chair[a] | 18.1 | 24.9 | 10.3 | <.001[b] |
| Time to walk[a] | 40.6 | 50.5 | 22.4 | <.001[b] |
| Time to bowel movement[a] | 25.2 | 37.3 | 18.1 | <.001[b] |
| Time to flatus[a] | 38.2 | 47.8 | 26.1 | <.001[b] |
| Time to defecation[a] | 76.4 | 88.1 | 61.7 | <.001[b] |
| Time to urination[a] | 47.4 | 65.6 | 24.7 | <.001[b] |
| Time to fluid tolerance[a] | 21.7 | 27.2 | 5.3 | <.001[b] |
| Time to food tolerance[a] | 44.8 | 71.7 | 11.1 | <.001[b] |
| Time to hunger[a] | 50.1 | 70.6 | 24.4 | <.001[b] |
| Time to libitum diet[a] | 73.2 | 111.0 | 26.0 | <.001[b] |
| Use of nasogastric tube | 22 (13.1) | 18 (21.2) | 4 (4.8) | .001[b] |
| Use of peritoneal drainage | 84 (50) | 52 (61.2) | 32 (38.6) | .004[b] |
| Postoperative ileus | 8 (4.8) | 7 (8.2) | 1 (1.2) | .029[b] |
| Intraoperative complications | 2 (1.2) | 2 (2.4) | — | .471 |
| Postoperative complications | 43 (25.6) | 28 (32.9) | 15 (18.1) | .027[b] |
|    I—II | 34 (20.2) | 20 (23.5) | 14 (16.9) | |
|    IIIa | 2 (1.2) | 2 (2.4) | — | |
|    IIIb | 6 (3.6) | 5 (5.9) | 1 (1.2) | |
|    IVa | 1 (0.6) | 1 (1.2) | — | |
|    IVb | — | — | — | |
| Anesthesiological complications | 16 (9.5) | 10 (11.8) | 6 (7.2) | .460 |
|    Pruritus (requiring medication) | 7 (4.2) | 3 (3.6) | 4 (4.8) | |
|    Limbs hyposthenia | 8 (4.8) | 7 (8.2) | 1 (1.2) | |
|    Dural puncture | 1 (0.6) | — | 1 (1.2) | |
| Readmission rate up to 30 d[a] | 9 (5.4) | 5 (5.9) | 4 (4.8) | .759 |

Values are presented as mean or number (percentage).

*ERAS*, enhanced recovery after surgery; *SPC*, standard perioperative care.

[a] Data missing for 1 patient in each group; [b]Statistically significant value.

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drainage and nasogastric tube, as expected from the ERAS guidelines.[25,26] Nonetheless, a major satisfaction of the patients was confirmed at 24 hours after surgery and at discharge, and these findings enforce the rationale behind the systematic application of the ERAS protocol items.

### Clinical implications
Successful implementation requires a multidisciplinary team, a willingness to change, and a clear understanding of the protocol. In addition, the difficulty in accomplishing necessary compliance with all protocol items calls for new implementation strategies, and in this perspective, the development of a randomized trial could be helpful. To date, there is a lack of clarity in the literature as to which ones of the single ERAS protocol item is linked with major benefits, and hence, systematic application of all these items is necessary to reach an optimal outcome. The use of novel analgesic strategies (TEA and intrathecal morphine) opens the quest for new analgesic standards in this type of surgery; in fact, because of the encouraging results of this study, the systematic adoption of TEA and intrathecal morphine was implemented in our institution, for open surgery and endoscopic surgery, respectively.

### Research implications
In our study, we demonstrated that the most relevant key elements of ERAS can be successfully applied to any setting of major gynecologic surgery, but a future prospective randomized study should investigate the role and impact of these items, particularly in very fragile patients. In fact, patients affected by ovarian cancer are often treated with chemotherapy or suboptimal surgery in case of augmented anesthesiological or surgical complication risk, but adoption of ERAS protocol might produce a therapeutic benefit by mitigation of adverse events. Nonetheless, opioid-sparing analgesia may be associated with better survival in patients with cancer,[27] and this is still not

benign condition or with explicit exclusion of patients with gynecologic malignancy. In our study, instead, we enrolled surgical candidates regardless of the type of gynecologic disease (except cervical cancer) and the surgical access, and we systematically assessed multiple parameters to report the impact of the ERAS protocol. An interesting finding is related to the successful adoption of TEA and intrathecal morphine that led to pain control with less use of parenteral analgesics and reduced use of total milliequivalent of opioids, without increasing the anesthesiological complications rate. PONV rates did not differ significantly during recovery, but we should note that the patients in the ERAS protocol group had a significant earlier resumed feeding with a reduced rate of POI. Furthermore, conversely to a recent publication,[11] in our study, we found a substantially reduced use of bowel preparation and placement of peritoneal

explored in the gynecologic setting. More recently, Schneider et al[28] proposed to incorporate a prehabilitation program (composed of exercise, nutritional support, and psychological interventions) to better optimize the psychophysical status of patients affected by advanced ovarian cancer who are candidates for surgery. Finally, the adoption of a minimally invasive approach by a few pioneers in the field of surgery for advanced ovarian cancer yields to a further reduction in the LOS and complication rates.[29]

### Strength and limitations

To our knowledge, this is one of the first randomized trials in gynecologic surgery including patients with both benign and oncological diseases. We adopted all the relevant key elements of an ERAS protocol, according to the known recommendation and emerging evidence, and innovatively adopted the concept of equianalgesia to monitor the actual opioid use. We conducted the study using prespecified subgroups and interaction tests. Furthermore, to decrease any potential biases, we adopted distinct teams of surgeons, anesthetists, and nurses, and we further minimized overlapping recovery of patients enrolled in the 2 study groups. Finally, we defined strict objective criteria for discharge, and we did not admit changes in the composition of the teams involved in the study.

In terms of limitations, we used strict inclusion and exclusion criteria, and these might not reflect the proportion of elder and fragile patients who were substantially excluded from the study. Finally, we cannot guarantee a total absence of a crossover effect from SPC to ERAS, although we tried to limit this scenario as much as possible.

### Conclusion

In conclusion, the validation of an ERAS protocol in a randomized setting seems to facilitate the adherence to the items with a significant reduction in LOS. The advantages of ERAS in gynecologic surgery have been strongly established, but there is still a need for large-scale,

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**TABLE 4**
**Single-item adherence in the ERAS group (compare prefix-oriented numeration with Supplemental Material)**

| Setting | Item description | Adherence rate, n/N (%) | |
|---|---|---|---|
| Preoperative | PRE.01 Thorough counseling | 83/83 (100.0) | |
| | PRE.02 Stop smoking | 6/8 (75.0) | |
| | PRE.03 Balanced relevant uncontrolled conditions | 13/17 (76.5) | |
| | PRE.04 Avoidance of bowel preparation | 79/83 (95.2) | |
| | PRE.05 Carbohydrate loading 12 h before surgery | 67/83 (80.7) | |
| | PRE.06 Carbohydrate snack 6 h before surgery | 13/83 (15.7) | |
| | PRE.07 Carbohydrate loading 2 h before surgery | 65/83 (78.3) | |
| | PRE.08. Antimicrobial prophylaxis | 83/83 (100.0) | |
| | PRE.09 Thromboembolism prophylaxis 12 h before surgery | 69/83 (83.1) | |
| | PRE.10 Avoidance of preanesthetic medications | 82/83 (98.8) | |
| Intraoperative | INTRA.01 Blended TIVA | 59/83 (71.1) | |
| | INTRA.02a TEA (longitudinal incision) | 29/34 (85.3) | 43/49 (87.6) |
| | INTRA.02b Intrathecal analgesic morphine (Pfannenstiel incision) | 14/15 (93.3) | |
| | INTRA.03a Intrathecal analgesic morphine (laparoscopic access) | 27/27 (100.0) | 34/34 (100.0) |
| | INTRA.03b TAP block (laparoscopy access) | 7/7 (100.0) | |
| | INTRA.04 TOF | 51/83 (61.4) | |
| | INTRA.05 Ventilation strategy | 83/83 (100.0) | |
| | INTRA.06. Multimodal PONV prevention | 82/83 (98.8) | |
| | INTRA.07 Lidocaine bolus and infusion | 76/83 (91.6) | |
| | INTRA.08 Intravenous magnesium sulfate | 74/83 (89.2) | |
| | INTRA.09 Goal-directed fluid therapy | 70/83 (84.3) | |
| | INTRA.10 Normothermia | 82/83 (98.8) | |
| | INTRA.11 Avoidance of nasogastric tube | 79/83 (95.2) | |
| | INTRA.12 Avoidance of peritoneal drainage | 51/83 (61.4) | |
| Postoperative | POST.01 Drinking water 4 h after surgery (d 0) | 74/83 (89.2) | |
| | POST.02 Light dinner the evening after surgery (d 0) | 54/83 (65.1) | |
| | POST.03 Chewing gum 3—4 h after surgery (d 0) | 74/83 (89.2) | |
| | POST.04 Chewing gum 6 h after surgery (d 0) | 71/83 (85.5) | |
| | POST.05 Mobilization in chair the evening after surgery (d 0) | 61/83 (73.5) | |
| | POST.06 Assisted deambulation in the morning (d 1) | 72/83 (86.7) | |
| | POST.07 Chewing gum in the morning (d 1) | 76/83 (91.6) | |
| | POST.08 Free light lunch (d 1) | 75/83 (90.4) | |
| | POST.09 Assisted deambulation in the afternoon (d 1) | 74/83 (89.2) | |
| | POST.10 Chewing gum in the afternoon (d 1) | 75/83 (90.4) | |

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**TABLE 4**
**Single-item adherence in the ERAS group (compare prefix-oriented numeration with Supplemental Material)** *(continued)*

| Setting | Item description | Adherence rate, n/N (%) |
|---|---|---|
| | POST.11 Free light dinner (d 1) | 77/83 (92.8) |
| | POST.12 Assisted deambulation in the evening (d 1) | 73/83 (88.0) |
| | POST.13 Early removal of Foley catheter (d 1) | 71/83 (85.5) |
| | POST.14 Opioid-sparing analgesia (d 0 and 1) | 76/83 (91.6) |

*d*, day; *ERAS*, enhanced recovery after surgery; *PONV*, postoperative nausea and vomiting; *TAP*, transversus abdominis plane; *TEA*, thoracic epidural analgesia; *TIVA*, total intravenous analgesia; *TOF*, train of four.

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multicenter randomized trials. Adequate comparisons of benefits of enhanced recovery in particular patients, namely, those affected by advanced ovarian cancer, are lacking and mostly related to the nonrandomized setting. ∎

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## Supplemental Material

We appreciate the opportunity provided by the *American Journal of Obstetrics and Gynecology* to present our Supplemental Material.

### Enhanced recovery after surgery protocol

We present the enhanced recovery after surgery (ERAS) protocol below subdivided into pre-, intra-, and postoperative sections. A prefix-oriented numeration is provided to easily compare the adherence rates of every single item presented in Table 4.

In the preoperative setting, a thorough counseling (PRE.01) about planned surgery and perioperative care is performed (between 30 and 20 days before surgery). In fact, a team composed of a surgeon, anesthesiologist, and nurse provides all the information about the measures that are going to be adopted and their practical actuation. The team discusses with the patient every item of the ERAS protocol, its rationale, and the level of patient's involvement and active collaboration requested and attended to obtain a measurable benefit. During the counseling, the baseline characteristics and comorbidities of the patients are registered. Patients are advised about the need to stop smoking (PRE.02) and optimization of relevant medical uncontrolled situations (ie, hypertension) with a specialist evaluation (PRE.03). Carbohydrate loading is advised the night before surgery (PRE.04). At the admission to the ward, patients do not receive bowel preparation (PRE.05), but patients are allowed to eat solid food up to 6 hours (PRE.06) and to drink clear fluids up to 2 hours before induction of anesthesia. Patients are encouraged to have a preoperative carbohydrate drink to help the body during the fasting perioperative hours (PRE.07). The carbohydrate load advised is a maltodextrin solution (12.6%) diluted in 200 mL of water. PRE.04 and PRE.07 amount to 400 and 200 mL, respectively. Thromboembolism prophylaxis (PRE.08) and antimicrobial prophylaxis (PRE.09) are used as per routine practice. Preanesthetic medications and preoperative intravenous hydration are avoided (PRE.10).

Intraoperative care is structured as follows. Blended anesthesia is mostly carried out using total intravenous anesthesia (INTRA.01) and short-acting medication with locoregional analgesia. In open surgery, we use thoracic epidural anesthesia for longitudinal incision (INTRA.02a) and intrathecal morphine for Pfannenstiel incision (INTRA.02b). Intrathecal morphine (INTRA.03a) is also adopted for a laparoscopic approach, whereas we use a transversus abdominis plane (TAP) block (INTRA.03b) in case of an unsuccessful location of a proper intervertebral space. Control of deep neuromuscular blocking with train-of-four stimulation is used to avoid residual paralysis (INTRA.04). A ventilation strategy using tidal volumes of 6 to 7 mL/kg with a positive end-expiratory pressure of 4 to 6 cm of water is used to reduce pulmonary complications (INTRA.05). A combination of multiple antiemetic drugs is used for multimodal prevention of postoperative nausea and vomiting (PONV) (according to preoperative assessment of the Apfel score) (INTRA.06). Induction of anesthesia is done by intravenous administration of lidocaine 1.5 mg/kg (INTRA.07) with magnesium 30 mg/kg (INTRA.08).[1] Continuous intravenous lidocaine perfusion of 2 mg/kg is performed until the discharge from the operating room. Goal-directed fluid resuscitation with a restrictive approach based on crystalloid isotonic balanced solution (avoiding saline solution 0.9%) and blood loss reintegration with colloids whenever possible (INTRA.09) and maintenance of intraoperative normothermia (INTRA.10) using suitable active warming devices are observed. Avoidance of nasogastric tube (INTRA.11) and peritoneal drainage (INTRA.12) is recommended.

During postoperative care, patients are actively proposed to start drinking clear fluid 4 hours after surgery (POST.01) and to start light eating the evening after surgery (POST.02). Chewing gum for at least 15 minutes 3 hours (POST.03) and 6 hours (POST.04), respectively, after surgery is proposed. Early mobilization in a chair is started from the evening of surgery (POST.05). On the first day after surgery, patients are assisted for active deambulation (POST 06). Chewing gum for at least 15 minutes 2 times a day, in the morning (POST.07) and in the afternoon (POST.10), is proposed. Patients are served a free light lunch (POST.08) and free light dinner (POST.11). Further assisted deambulation in the afternoon (POST.09) and in the evening (POST.12) is also proposed. Vesical Foley catheter is removed as soon as the patient is able to move out of the bed (POST.13). Postoperative pain control is obtained with opioid-sparing strategies (namely, we avoid the use of parenteral opioids, POST.14), using acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), to avoid a postoperative ileus and reduce PONV. In detail, parenteral acetaminophen (1000 mg) is administered every 8 hours for 32 hours, whereas parenteral NSAIDs (ketoprofen, 100 mg) are administered every 12 hours for 48 hours; afterward, the same drugs are used per os. In case of subsequent breakthrough pain, an extra dose of parenteral acetaminophen therapy is administered, and if not efficacious, a dose of parenteral NSAIDs is administered.

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### SUPPLEMENTAL FIGURE 1
**Rates of reported nausea at 0, 3, 6, 12, and 24 hours after surgery**
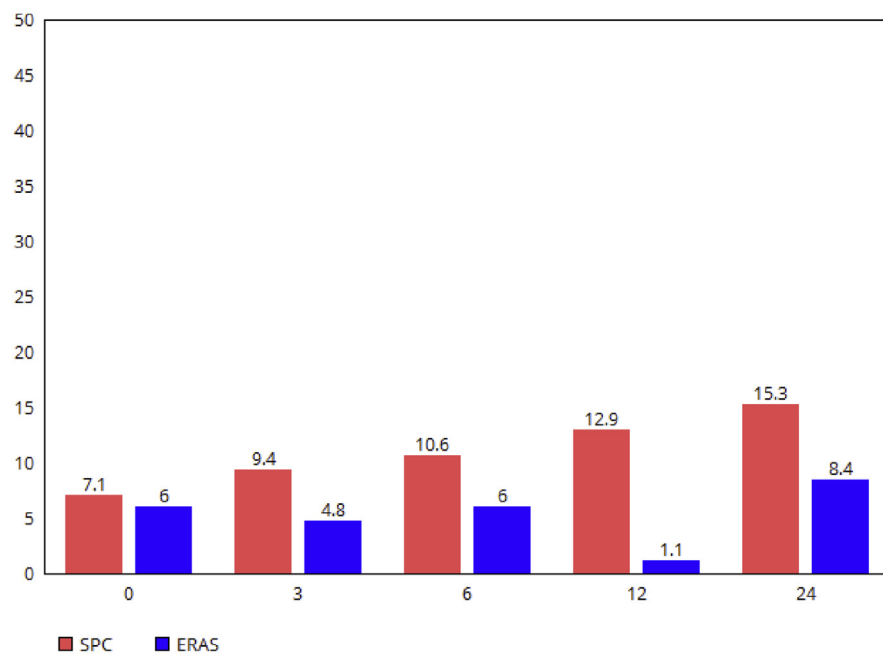


ERAS, enhanced recovery after surgery; SPC, standard perioperative care.

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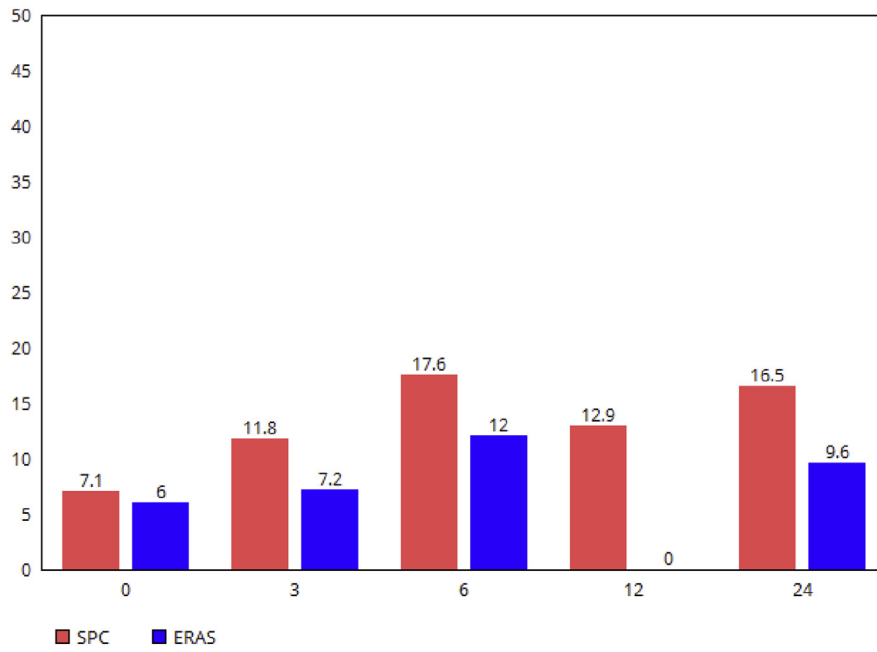
### SUPPLEMENTAL FIGURE 2
**Rates of vomiting event at 0, 3, 6, 12, and 24 hours after surgery**
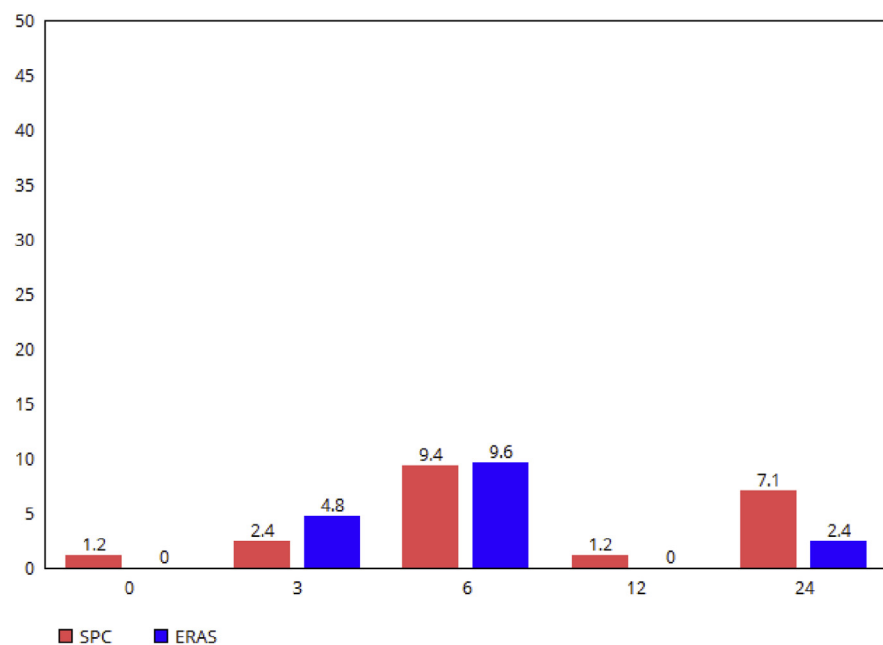


ERAS, enhanced recovery after surgery; SPC, standard perioperative care.

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**SUPPLEMENTAL FIGURE 3**
**Rates of postoperative nausea and vomiting at 0, 3, 6, 12, and 24 hours after surgery**



ERAS, enhanced recovery after surgery; SPC, standard perioperative care.

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**SUPPLEMENTAL FIGURE 4**
**Rate of optimal pain control (numeric rating scale <1) at 0, 3, 6, 12, and 24 hours after surgery**
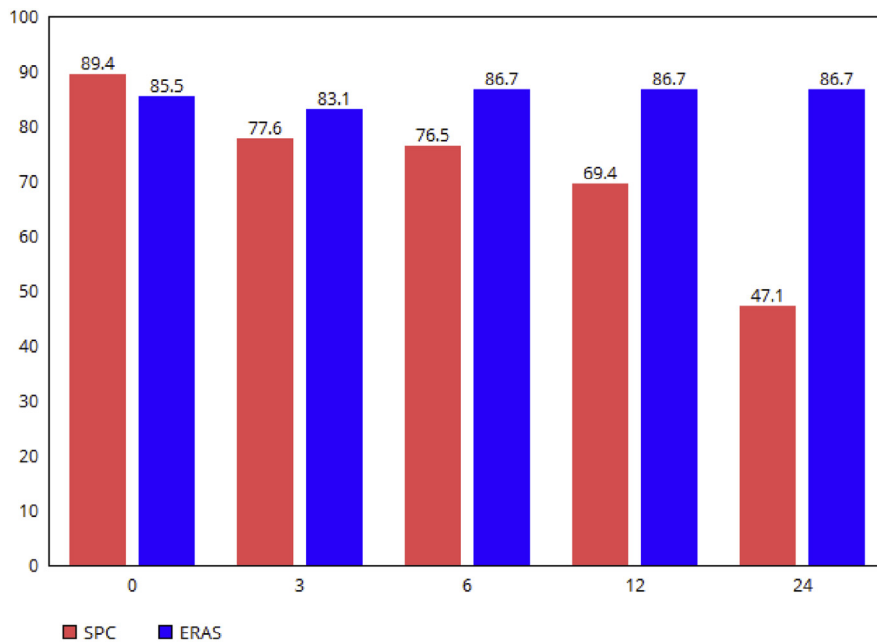


ERAS, enhanced recovery after surgery; SPC, standard perioperative care.

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**SUPPLEMENTAL TABLE**
**Item comparison between SPC and ERAS**

| Setting | Item description | SPC | ERAS |
|---|---|---|---|
| Preoperative | PRE.01 Thorough counseling | — | Yes |
| | PRE.02 Stop smoking | — | Yes |
| | PRE.03 Balanced relevant uncontrolled medical conditions | — | Yes |
| | PRE.04 Avoidance of bowel preparation | — | Yes |
| | PRE.05 Carbohydrate loading 12 h before surgery | — | Yes |
| | PRE.06 Carbohydrate snack 6 h before surgery | — | Yes |
| | PRE.07 Carbohydrate loading 2 h before surgery | — | Yes |
| | PRE.08. Antimicrobial prophylaxis | Yes | Yes |
| | PRE.09 Thromboembolism prophylaxis 12 h before surgery | Yes | Yes |
| | PRE.10 Avoidance of preanesthetic medications | — | Yes |
| Intraoperative | INTRA.01 Blended TIVA | — | Yes |
| | INTRA.02a TEA (longitudinal incision) | — | Yes |
| | INTRA.02b Intrathecal analgesic morphine (Pfannenstiel incision) | — | Yes |
| | INTRA.03a Intrathecal analgesic morphine (laparoscopic access) | — | Yes |
| | INTRA.03b TAP block (laparoscopic access) | — | Yes |
| | INTRA.04 TOF | — | Yes |
| | INTRA.05 Ventilation strategy | — | Yes |
| | INTRA.06. Multimodal PONV prevention | — | Yes |
| | INTRA.07 Lidocaine bolus and infusion | — | Yes |
| | INTRA.08 Intravenous magnesium sulfate | — | Yes |
| | INTRA.09 Goal-directed fluid therapy | — | Yes |
| | INTRA.10 Normothermia | Yes | Yes |
| | INTRA.11 Avoidance of nasogastric tube | — | Yes |
| | INTRA.12 Avoidance of peritoneal drainage | — | Yes |
| Postoperative | POST.01 Drinking water 4 h after surgery (d 0) | — | Yes |
| | POST.02 Light dinner the evening after surgery (d 0) | — | Yes |
| | POST.03 Chewing gum 3—4 h after surgery (d 0) | — | Yes |
| | POST.04 Chewing gum 6 h after surgery (d 0) | — | Yes |
| | POST.05 Mobilization in a chair the evening after surgery (d 0) | — | Yes |
| | POST.06 Assisted deambulation in the morning (d 1) | — | Yes |
| | POST.07 Chewing gum in the morning (d 1) | — | Yes |
| | POST.08 Free light lunch (d 1) | — | Yes |
| | POST.09 Assisted deambulation in the afternoon (d 1) | — | Yes |

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**Item comparison between SPC and ERAS** (continued)

| Setting | Item description | SPC | ERAS |
|---|---|---|---|
| | POST.10 Chewing gum in the afternoon (d 1) | — | Yes |
| | POST.11 Free light dinner (d 1) | — | Yes |
| | POST.12 Assisted deambulation in the evening (d 1) | — | Yes |
| | POST.13 Early removal of Foley catheter (d 1) | — | Yes |
| | POST.14 Opioid-sparing analgesia (d 0 and 1) | — | Yes |

*d*, day; *ERAS*, enhanced recovery after surgery; *PONV*, postoperative nausea and vomiting; *SPC*, standard perioperative care; *TAP*, transversus abdominis plane; *TEA*, thoracic epidural analgesia; *TIVA*, total intravenous analgesia; *TOF*, train of four.

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