

Effects of intraoperative PEEP on postoperative pulmonary complications in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer: study protocol for a randomized controlled trial

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Study protocol

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Abstract

Background: There are increasing studies shown that the use of a lung-protective ventilation strategy has a lung protection effect in patients undergoing abdominal surgery, however, the appropriate PEEP has not yet defined. Adopting a suitable PEEP may prevent PPCs. Robot-assisted laparoscopic surgery is the newest and most minimally invasive care for bladder cancer or prostate cancer. It is also necessary to consider the effects of trendelenburg position with pneumoperitoneum (PnP) on airway pressure and pulmonary function. The role of PEEP during the intraoperative period in preventing PCC for robot-assisted laparoscopic surgery is not clearly defined. Methods/design: A total number of 208 patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer will be enrolled and randomized into a standard PEEP (6-8 cmH₂O) group and a low PEEP (≤ 2 cm H₂O) group. Both groups will receive an inspired oxygen fraction (FiO₂) of 0.50 and a tidal volume of 8 ml/kg ideal body weight (IBW). Standard perioperative fluid management standardization and analgesic treatments will be applied in both groups. The primary endpoint was postoperative pulmonary complications within 7 days after surgery. Secondary endpoints will be: the modified clinical pulmonary infection score (mCPIS), postoperative extrapulmonary complications, postoperative surgical complications, intensive care unit (ICU) length of stay, hospital length of stay, thirty-day mortality. Discussion: This trial is aimed to assess the effects of low tidal volumes combined a intraoperative PEEP ventilation strategy on postoperative pulmonary complications in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

Background

Robot-assisted laparoscopic surgeries including Robot-assisted laparoscopic radical prostatectomy (RALP) and Robot-assisted laparoscopic radical cystectomy (RARC) are the newest and most minimally invasive care for bladder cancer or prostate cancer [1]. The incidence of postoperative pulmonary complications (PPCs) in patients undergoing general surgery is approximately 5% and 12% to 58% of patients undergoing abdominal surgery will develop a PPC [3, 4]. Furthermore, PPCs are strongly associated with prolonged postoperative hospital stays and a higher risk of mortality [5-7].

Nearly 30% of surgery patients undergoing general anesthesia and mechanical ventilation are at intermediate to high risk for PPCs according to large cohort studies [4, 8]. Both alveolar overstretching and atelectasis induce the release of inflammatory mediators, leading to lung and systemic organ damage [9]. Lung-protective ventilation including the use of low tidal volumes and positive endexpiratory pressure (PEEP), aims to prevent atelectasis and improve gas exchange [10, 11]. Furthermore, PEEP has been found to reduce mortality in patients with the acute respiratory distress syndrome [12].

Adopting an appropriate PEEP may prevent PPCs. When high PEEP is applied, alveolar may overinflated and pulmonary vascular resistance is likely to increase; however, use of low PEEP may not prevent atelectasis [9]. Compared with nonprotective mechanical ventilation without PEEP, a number of studies have shown that the use of a lung-protective ventilation strategy has a lung-protective effect in patients

with healthy lungs who are undergoing abdominal surgery, reducing the incidence of PPC [13, 14]. Despite all these studies recommending the use of low tidal volume [9, 13-17], the appropriate PEEP has not yet been defined. A multicenter observational study showed that approximately 20% of patients did not receive PEEP during routine anesthetic practice [16]. In the Intraoperative Protective Ventilation (IMPROVE) trial, a lung-protective ventilation strategy with lower tidal volumes and PEEP of 6 cm H₂O was associated with improved clinical outcomes in patients undergoing major abdominal surgery [13]. Furthermore, a protective ventilation strategy with 10 cm H₂O PEEP improved respiratory function and reduced the modified clinical pulmonary infection score (mCPIS) in another study including patients undergoing abdominal nonlaparoscopic surgery [14]. However, another study showed that low tidal volume combined low PEEP (3 cm H₂O) ventilation may increase the risk of PCCs during major surgery such as hepatectomy [17]. In the PROVHILLO trial, a ventilation strategy of high PEEP (12 cm H₂O) did not reduce the incidence of PPCs, but more likely caused haemodynamic instability in patients undergoing open abdominal surgery [15]. Therefore, the authors suggested a ventilation strategy of low tidal volume combined with low PEEP (≤ 2 cm H₂O).

It should also be noted that all these studies included only open surgeries or various types of abdominal surgery; they did not include patients planning to undergo robot-assisted laparoscopic surgery. Furthermore, it is also necessary to consider the effects of steep Trendelenburg (sT) positioning and pneumoperitoneum (PnP) on airway pressure and pulmonary function [18], which can increase intra-abdominal pressure and enhance the cranial displacement of the diaphragm. This displacement will decrease lung compliance, lung volumes and increase lung resistance. It has been recommended to adopting a PEEP of 7 cmH₂O during RALP, which could improve arterial oxygenation without causing excessive peak airway pressure [19]. Also a lung-protective ventilation strategy with a lower tidal volume (VT) of 6 mL/kg and 8 cm H₂O PEEP was associated with less impaired postoperative pulmonary functions in patients undergoing RALP in another recent study [20].

The role of PEEP during the intraoperative period in preventing PCC for robot-assisted laparoscopic surgery has not been clearly defined. This study may further improve our knowledge regarding the effects of intraoperative PEEP on postoperative pulmonary complications, survival rates and in-hospital stays in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

Methods And Design

Objectives of the study:

This trial aimed to compare the effects of low tidal volumes combined with standard PEEP (6-8 cmH₂O) to those of low PEEP (≤ 2 cm H₂O) in patients at risk for complications undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer during general anesthesia in terms of: (1) PPCs, (2) mCPIS score, postoperative extrapulmonary complications, changes in chest X-ray findings and oxygenation; (3) intraoperative complications including hypoxemia, hypotension and

massive transfusion; and (4) postoperative surgical complications, intensive care unit (ICU) lengths of stay, hospital lengths of stay and thirty-day mortality.

Study design: This is an unfunded, parallel-group, double-blinded, prospective, randomized controlled clinical trial was registered at <http://www.chictr.org.cn> (ChiCTR1800019867) and was conducted at the Department of Anesthesiology and Intensive Care of Zhejiang Provincial People's Hospital. The first patient will be randomized in January 2019. This trial protocol is conducted according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines (Figure 1). The SPIRIT 2013 Checklist is given in Additional file 1.

Blinding, data collection, randomization and recordkeeping

Selection of the participants

Researchers will be trained prior to investigation. Study data including patient clinical characteristics, intraoperative respiratory parameters, postoperative outcomes, and laboratory test will be collected onto case report forms (CRF) (Additional file 2).

An independent researcher will randomize the participants into the study group (standard group PEEP) and control group (low PEEP group) in a ratio of 1:1. The random sequence will be computer-generated and participants will be allocated in numerical order with sealed opaque envelopes. The attending anesthesiologist performs anesthesia strictly according to the research protocol and is also responsible for data during the preoperative, intraoperative and PACU period. The chief surgeon performs the postoperative laboratory testing. An independent researcher will be involved in postoperative follow-up and data collection. Statistical analysis will be performed by a statistician who does not participate in the data collection. Patients, research staff, surgeons, intensive care physicians and the statistician will be unaware of the group allocation. Some preoperative characteristics and laboratory results will automatically derived from a computer data base.

The original data (CRF and relevant records) will be maintained for 10 years and then destroyed according to hospital standards.

Selection of the participants

Patients scheduled for elective robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer under general anesthesia will be screened and recruited during preoperative assessment. Patients meeting inclusion criteria will be required to provide their written informed consent. The participant can withdraw from the trial at any time.

Inclusion criteria are patients older than 18 y, American Society of Anesthesiologists (ASA) physical status I - III, body mass index (BMI) between 18-35 kg/m².

Exclusion criteria are emergency surgery or history of previous lung surgery, history of mechanical ventilation within the 2 weeks before recruitment, non-invasive ventilation or oxygen therapy at home, acute respiratory failure (pneumonia, acute lung injury or acute respiratory distress syndrome), history of chronic obstructive pulmonary disease (COPD), persistent hemodynamic instability or severe cardiac disease (New York Heart Association class III or IV, or persistent ventricular tachyarrhythmias, or acute coronary syndrome), sepsis or septic shock, need renal replacement therapy (CRRT), progressive neuromuscular illness, pregnancy, participation in another study or refusal to participate.

Time course of the study

Preoperative admission

Medical history, ASA physical status, BMI, 12-lead ECG, laboratory results, chest X-ray or computed tomography (CT) scan, ARISCAT score (the Assess Respiratory Risk in Surgical Patients in Catalonia study, the Additional file 3) and nutritional risk screening (NRS 2002 tool), the results of echocardiography and spirometry (in cases of history of coronary artery disease or smoking) will be recorded.

Intraoperative care

A central venous catheter and an arterial cannula will be placed before induction of anesthesia. Peripheral oxygen saturation (SpO₂), arterial blood pressure, heart rate (HR), ECG, end-tidal carbon dioxide tension (EtCO₂) and bispectral index (BIS) will be monitored continuously. Pneumoperitoneum (PnP), tidal volume, PEEP, airway pressures including peak pressure and plateau pressure, airway resistance (Raw), V_ds/V_t, core temperature, and arterial blood gas analysis data will be recorded.

Crystalloid (12-15ml/kg/h) was infused to maintain hemodynamic stability and central venous pressure 5-12 cm H₂O. Blood loss and vasodilation was supplemented by colloidal fluid.

Routine anesthesia was induced with intravenous dexmedetomidine (1 µg/kg) or midazolam (0.05-0.075mg/kg), cisatracurium (2 mg/kg), propofol (2-3 mg/kg) and fentanyl (1-3 µg/kg) for tracheal intubation. Anesthesia was maintained with propofol, sevoflurane and remifentanyl infusion to maintain the BIS 40-50 until skin suturing was completed. Cisatracurium (1.0-1.5 mg/kg) is administered every hour and is adjusted according to the anesthesiologist's decision.

Ropivacaine is administered as local anesthetic before and at the end of operation respectively. Fentanyl (1-3 µg/kg) and flurbiprofenaxetil 50 mg are required before remifentanyl is stopped.

Postoperative care

Patients will be transferred to the post anesthesia care unit (PACU) after surgery regardless of whether they are still intubated.

Postoperative pain management will be suggested to achieve a visual analogue scale (VAS) pain score of < 3/10 using a patient-controlled intravenous analgesia pump including fentanyl (0.3-0.5 µg/kg),

flurbiprofenaxetil (100 mg) and palonosetron hydrochloride (0.25 mg) palazidine.

The ICU physician and surgeon will independently monitor clinical progress and all endpoints by daily physical examinations. Appropriate prophylactic antibiotics and antithrombotic treatments will be administered as required during the postoperative period. Chest X-ray or CT scanning will be performed when clinically indicated. Arterial blood gas analysis will be performed on POD 1 and POD 3 and other laboratory tests will be performed on POD 1, POD 3, POD 5 and POD 7. The examinations will be repeated and microbiology tests will be performed when the development of pulmonary complications are suspected.

Study arms and intraoperative ventilation protocol

Patients will be randomly assigned to with the low PEEP ventilation group (PEEP \leq 2 cm H₂O) or the standard PEEP group (PEEP = 6-8 cm H₂O) using a volume-controlled ventilation strategy (Datex Ohmeda S/5 Avance; GE Healthcare, Helsinki, Finland) with a tidal volume of 8 ml/kg ideal body weight (IBW), an inspired oxygen fraction (FiO₂) of 0.50 and inspiratory to expiratory ratio of 1:2. Respiratory rate should be adjusted to maintain ETCO₂ between 35 and 45 mmHg) and plateau pressure should be no more than 30 cmH₂O. IBW is calculated with formulas as follows [13]: $45.5 + 0.91 \times (\text{centimeters of height} - 152.4)$ for females and $50 + 0.91 \times (\text{centimeters of height} - 152.4)$ for males. Recruitment maneuvers (RMs) [21] will be performed immediately after tracheal intubation and every time ventilator is interrupted until the end of surgery in each group. The compliance of the respiratory system will be calculated with the formulas of $VT / (\text{plateau pressure of the respiratory system} - \text{PEEP})$.

Recruitment maneuvers will be performed as follows:

- (1). Pressure support ventilation (PSV) mode
- (2). Positive end-expiratory pressure (PEEP) set to 30 cm of water
- (3). Inspiratory gas flow set to the highest value
- (4). Duration of the maneuver = 30 sec

A rescue therapy will be applied in case of desaturation (defined as a peripheral SpO₂ of less than 92%), consisting of increased FiO₂ to 100% in each group and increasing PEEP in the low PEEP group (Additional file 4).

Study endpoints

Primary outcome measure

The primary endpoint was PPCs including new atelectasis or infiltrates on a chest X-ray or CT scanning, respiratory failure defined as the need for noninvasive or invasive ventilation or partial pressure of arterial oxygen/fraction of inspired oxygen (PaO₂/FiO₂) < 300 within 7 days after surgery [21].

Secondary outcome measures

Secondary outcome variables were any pulmonary complications and extrapulmonary complications as follows (Additional file 5):

1. Intraoperative complications: pneumothorax confirmed by chest X-ray and any other complications.
2. Postoperative pulmonary complications (PPCs) within 30 days after surgery. Those PPCs are scored according to a grading scale ranging from 0 to 4 [22] (grade 0 representing no PPCs and grades 1 to 4 representing gradually worse forms of PPCs) within 7 and 30 days after surgery (Table 1).
3. Postoperative pulmonary complications will also be analyzed separately (Table 1).
 - (1) Pneumonia is defined according to Centers for Disease Control (CDC) criteria [23];
 - (2) Purulent sputum;
 - (3) Postoperative hypoxemia and severe hypoxemia [24];
 - (4) Suspected pulmonary infection is described in a previous study [15];
 - (5) Pulmonary infiltrate is defined according to consensus guidelines[25]: Chest X-ray demonstrating monolateral or bilateral infiltrate.
 - (6) Atelectasis, pleural effusion or pneumothorax are identified by chest X-ray.
 - (7) The modified clinical pulmonary infection score (mCPIS) is calculated as previously described [26] (Table 2).
 - (8) Suspected pulmonary complications [14];
 - (9) Requirement for postoperative ventilation (respiratory failure that requires noninvasive and/or invasive ventilation) for at any time after surgery according to standard criteria and clinical practice guidelines [22].
4. Postoperative extrapulmonary complications within 30 days after surgery:
 - (1) Systemic inflammatory response syndrome (SIRS) criteria [12];
 - (2) Sepsis and severe sepsis [12];
 - (3) Septic shock [12];
 - (4) Other extrapulmonary infection including surgical site infection (SSI) [27] and intraabdominal abscess;

(5) Need for postoperative blood transfusion.

(6) Postoperative surgical complications: anastomotic leakage and need for surgical reintervention, defined according to consensus criteria [28].

(7) Unexpected intensive care unit (ICU) admission or readmission.

(8) ICU length of stay and hospital length of stay.

(9) Hospital free-days at follow-up day 30.

(10) In-hospital mortality and thirty-day mortality (all-cause mortality 30 days after randomization).

From postoperative day 7 (POD 7 to POD 30, follow-up)

Secondary endpoints and any mortality will also be evaluated during the follow-up period. The CONSORT flowchart of the trial is shown in Figure 2.

Data monitoring and Handling of implausible values or missing values: A clinical investigator will identify implausible values. Missing continuous variables should be less than 10% and will be replaced by median. Missing values will be replaced by the mean of all plausible data (both groups) of the respective endpoint. Data monitoring is managed by an independent investigator who is not involved in the study. The progress of the study will be evaluated and the completeness and accuracy of the data (Informed Consent Forms, source data, CRF and outcome variables) will be verified.

Statistics:

Normally distributed variables will be expressed as the mean \pm standard deviation (SD) and will be compared with the Student's t-test. Categorical variables will be compared using the chi-square test or the Fisher's exact test. Non-normal continuous variables will be expressed as median (interquartile range (IQR)) and evaluated with the Mann-Whitney U-test. Intention-to-treat (ITT) analyses are performed to compare the composite outcome measure at 7 days in the two groups by the chi-squared test (or Fisher's exact test as appropriate) and multiple logistic regression analysis adjusting will be performed to identify various risk factors (for the primary outcome and the pulmonary complications at postoperative Day 30). Adjusted analyses were performed with the use of robust Poisson generalized-linear-model regression for continuous outcomes and are presented as relative risks with 95% confidence intervals. $P < 0.05$ will be considered statistically significant and all reported p values will be 2-sided. Interim analysis of safety will be conducted after enrolment of the first 200 patients. All analyses will be conducted using the SPSS Version 18.0 (SPSS, Chicago, IL, USA) software.

Sample size calculation

The incidence rate of postoperative pulmonary complications was 39% in the low PEEP group [15]. Two tailed chi-squared test was performed and we estimated that 188 patients were required to provide 90%

power to detect a 50% relative difference between the two groups (39% to 20%), with a type I error probability of 0.05. Assuming that follow-up lost rate was 10 %, and then a total of 208 cases are needed. Analysis was computed using G-Power (version 3.1; Informer Technologies, Inc.).

Adverse events and interruption of the trial:

All patients will be continuously monitored during the study including daily visits during in-hospital and daily phone-call visits during the out of hospital follow-up period (until POD 30). All serious adverse, unexpected or possibly related events will be recorded in the CRF and will be reported to the data monitoring and safety committee (DMSC). DMSC will recommend that the study must be stopped unless there is evidence that patient will safety (a between-group difference in serious adverse events or in 30-day mortality is found).

Discussion

In this pragmatic, prospective, randomized controlled trial of patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer, our aim will not be only to assess possible single effects of PEEP levels on major PPCs from those of lower tidal volumes and RM, but also to assess relevant clinical parameters associated with alterations in pulmonary function such as chest X-ray, abnormalities, mCPIS, arterial oxygenation/peripheral oxygen saturation in air and changes in dyspnea/cough/secretions. Our findings might change current practice of mechanical ventilation in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

Notably, mechanical ventilation itself is one of major contributors to PPCs [29]. Also sT positioning together with pneumoperitoneum is also an important risk factor for PPCs [30]. Intraabdominal pressure is frequently higher than airway pressure during PnP with carbon dioxide (CO₂) for laparoscopic surgery. This pressure gradient usually causes cephalad displacement of the diaphragm and collapses adjacent pulmonary tissues. PnP also decreases respiratory compliance and arterial oxygenation [31]. All these influences on PnP lead finally to atelectasis [32]. The major difference between robot-assisted surgeries and other laparoscopic surgeries is the sT positioning, which will further decrease respiratory compliance and vital capacity.

On the other hand, PEEP is thought to prevent the development of atelectasis by keeping the airways open and maintaining adequate gas exchange at the end of the expiratory period during PnP [9]. Certainly, the level of PEEP should be adopted according to the patient's and surgical characteristics, as well as to the patient's positioning.

The optimal PEEP has not yet been defined in patients undergoing robot-assisted laparoscopic surgery even though it is recommended to adopting PEEP of over 5 cm H₂O in patients undergoing laparoscopic surgery [11]. One study recommended to adopting a PEEP of 7 cmH₂O during RALP[19], another recent study found that 8 cm H₂O PEEP was the optimal level of PEEP in patients undergoing RALP[20]. As we know that very low levels of PEEP are potentially associated with atelectasis by promoting repeated

opening and closing of small airways [33]. However, higher levels of PEEP may increase mean airway pressure of the respiratory system and likely even impair hemodynamics.

There is an increasing number of highly qualitative Randomized Controlled Trials (RCTs) regarding intraoperative mechanical ventilation and PPCs both in abdominal surgeries [10, 11] and laparoscopic surgeries[32], whereas direct assessment of the effect in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer remains lacking. The potential significance of this trial is that it may provide evidence of the effects of intraoperative PEEP on postoperative pulmonary complications in patients undergoing robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer.

There are some potential strengths of the present trial protocol. First, the included patients will undergo elective robot-assisted laparoscopic radical resection for bladder cancer or prostate cancer with longer anesthesia duration, which is potential risk factor of PPCs [7]. Second, this trial design includes instructions for fluid management standardization and analgesic treatments during the perioperative period. Third, the adopting ARISCAT score is considered to be the most valuable tool for predicting PPCs, although various scores have been developed for predicting PPCs incidence based on various countries and surgical populations, [9].

Trial status

The study protocol version number was (V1.0, September 10, 2018). It was first submitted to the Ethics Committee of Zhejiang Provincial People,s Hospital (People,s Hospital of Hangzhou Medicine College) on 10 September 2018 and finally approved on 22 October 2018. The first participant is expected to be recruited before March 2019 and the estimated completion date of recruitment will be October 2021.

Abbreviations

ABGa: Arterial blood gas analysis; ALI: Acute lung injury; ARDS: Acute respiratory distress syndrome; AMI: Acute myocardial infarction; ASA: American Society of Anesthesiologists; BIS: bispectral index; BMI: Body Mass Index; CDC: Centers for Disease Control; CO₂: carbon dioxide; COPD: Chronic obstructive pulmonary disease; CRF: Case Report Form; CRRT: renal replacement therapy; CT: Computer tomography; DMSC: data monitoring and safety committee; DIC: Disseminated intravascular coagulation; ECG: Electrocardiogram; EtCO₂: End-tidal carbon dioxide tension; FiO₂: Fraction of inspired oxygen; HR: Heart rate; IBW: Ideal bodyweight; ICU: Intensive care unit; IQR: interquartile range; LAG: laparoscopic surgery; mCPIS: modified clinical pulmonary infection score; PACU: Post-anesthesia Care Unit; PaO₂: Partial pressure of arterial oxygen; PEEP: Positive end-expiratory pressure; PnP: pneumoperitoneum; POD: Postoperative day; PPC: Postoperative pulmonary complications; PSV: Pressure Support Ventilation; RALP: Robot-assisted laparoscopic radical prostatectomy; RARC: Robot-assisted laparoscopic radical cystectomy; Raw: Airway resistance; RM: Recruitment maneuver; SD: Standard deviation; SIRS: Systemic inflammatory response syndrome; SPIRIT: Standard Protocol Items: Recommendation for Interventional

Trials; SpO₂: Oxygen saturation; SSI: surgical site infection; sT: Trendelenburg; VAS: visual analogue scale; V_ds/V_t: Dead space fraction; VT: tidal volumes; WBC: White Blood Cell.

Declarations

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Availability of data and materials

Not applicable.

Authors' contributions

ZHOU ZF and HU SF designed the study protocol and wrote the paper. WANG HF and ZHANG MZ designed the statistical method. The work of patient recruitment and data collecting will be done by FANG JB, YU YJ, WANG WY, Chen L and CHEN JB. HU SF is the study director and FANG JB is the principal investigator of this study. All authors have read the manuscript and approved to submitting the final paper.

Authors' information

Not applicable.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Zhejiang Provincial People's Hospital (People's Hospital of Hangzhou Medicine College) (registration number KY2018027) on 22 October 2018. Any subsequent protocol and informed consent document amendments must be approved by the responsible of Ethics Committee. All communications with the regulatory authorities and the Ethics Committee must be recorded.

All recruited patients will be informed of the trial purposes and their duties within the trial before randomization. Informed consent will be obtained from all study participants. Recruited patients can withdraw from the study at any time without providing any specific reason. The patient data will be stored in a separate, safe place but that it may be reviewed by the relevant investigator.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

1. Grade scale for postoperative pulmonary complications.

e	Detailed description
e	- Cough, dry
	- Microatelectasis: abnormal lung findings and temperature > 37.5°C without other documented cause; results of chest radiograph either normal
	- Dyspnea, not due to other documented cause
e	- Cough, productive, not due to other documented cause
	- Bronchospasm: new wheezing or pre-existent wheezing resulting in change therapy
	- Hypoxemia
	- Atelectasis: radiological confirmation plus either temperature > 37.5°C or abnormal lung findings
	- Hypercarbia, transient, requiring treatment, such as naloxone or increased manual or mechanical ventilation
e	- Pleural effusion, resulting in thoracentesis
	- Pneumonia, suspected: radiological evidence without bacteriological confirmation
	-Pneumonia, proved: radiological evidence and documentation of pathological organism by Gram stain or culture
	- Pneumothorax
	- Re-intubation postoperative or intubation, period of ventilator dependence (non-invasive or invasive ventilation) ≤ 48 hours
e	Ventilatory failure: postoperative non-invasive ventilation dependence ≥ 48 hours, or re-intubation with subsequent period of ventilator dependence ≥ 48 hours

Table 2. The definition of modified Clinical Pulmonary Infection Score (mCPIS).

Items	CPIS Points		
	0	1	2
Tracheal secretions	Rare	Abundant	Abundant + purulent
Chest X-ray infiltrates	No infiltrate	Diffused	Localized
Temperature (°C)	36.5- 38.4	38.5- 38.9	≤ 36.5 or ≥ 39.0
Leukocytes count (per mm ³)	4,000- 11,000	<4,000 or >11,000	< 4,000 or > 11,000 + band forms ≥ 500
PaO ₂ /FiO ₂ ,(mm Hg)	> 240 or ARDS		≤ 240 and no evidence of ARDS
Microbiology	Negative		Positive

PaO₂ =Partial pressure of arterial oxygen; FiO₂ =Fraction of inspired oxygen; ARDS =Acute respiratory distress syndrome

Figures

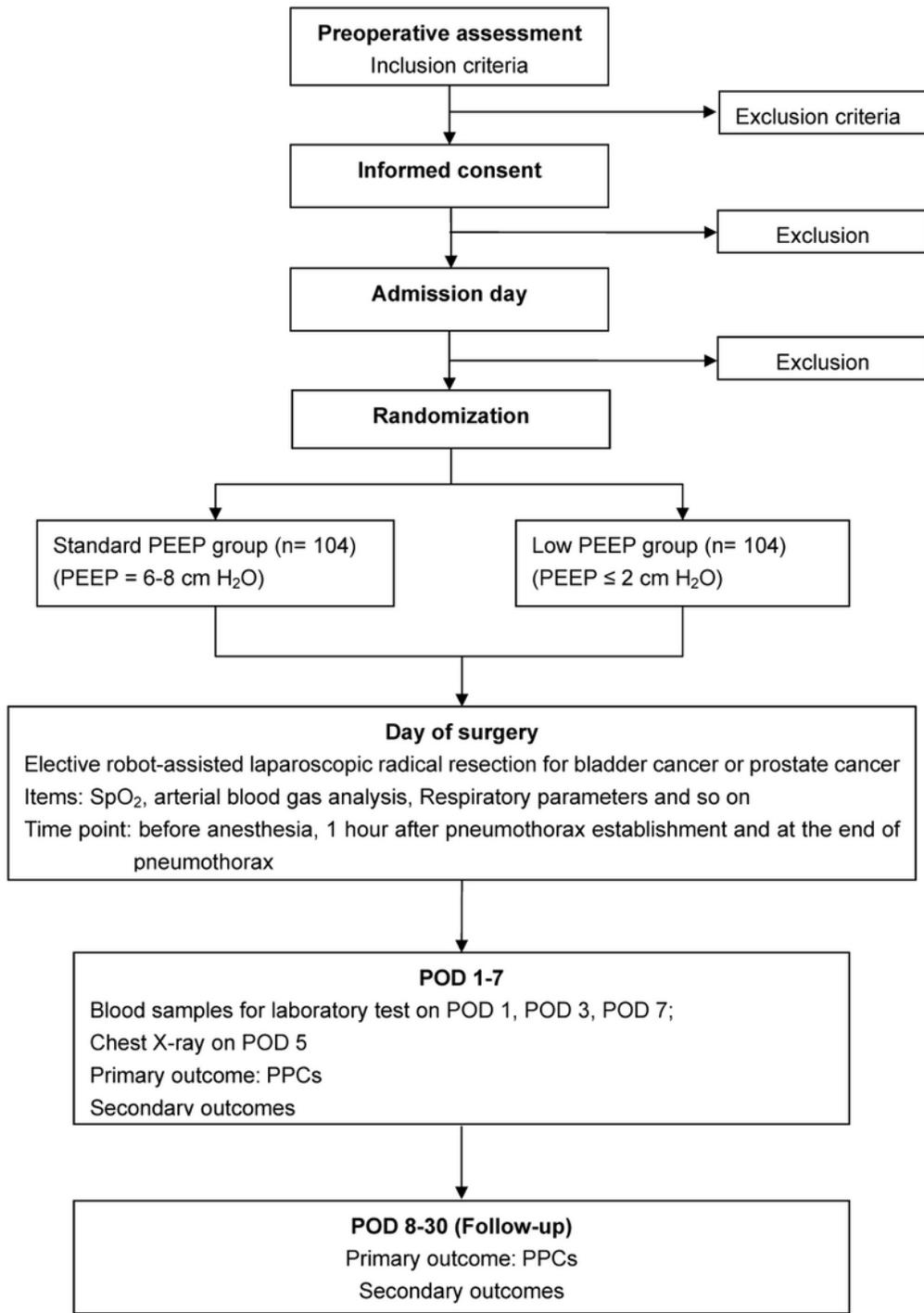


Figure 2

The CONSORT flowchart of the trial.

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