Robotic-assisted versus conventional laparoscopic surgery in the management of obese patients with early endometrial cancer in the sentinel lymph node era: a randomized controlled study (RObese)

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ABSTRACT

Background Nearly 65% of patients with endometrial cancer who undergo primary hysterectomy have concurrent obesity. Retrospective data show advantages in using robotic surgery in these patients compared with conventional laparoscopy, namely lower conversion rate, increased rate of same-day discharge, and reduced blood loss. Nevertheless, to date no prospective randomized controlled trials have compared laparoscopic surgery versus robotic-assisted surgery in morbidly obese patients.

Primary Objective The robotic-assisted versus conventional laparoscopic surgery in the management of obese patients with early endometrial cancer in the sentinel lymph node era: a randomized controlled study (RObese) trial aims to find the most appropriate minimally invasive surgical approach in morbidly obese patients with endometrial carcinoma.

Study Hypothesis Robotic surgery will reduce conversions to laparotomy in endometrial cancer patients with obesity compared with those who undergo surgery with conventional laparoscopy.

Trial Design This phase III multi-institutional study will randomize consecutive obese women with apparent early-stage endometrial cancer to either laparoscopic or robot-assisted surgery.

Major Inclusion/Exclusion riteria The RObese trial will include obese (BMI≥30 kg/m^2) patients aged over 18 years with apparent 2009 Federation of Gynecology and Obstetrics (FIGO) stage IA-IB endometriod endometrial cancer.

Primary Endpoint Conversion rate to laparotomy between laparoscopic surgery versus robot-assisted surgery.

Sample Size RObese is a superiority trial. The clinical superiority margin for this study is defined as a difference in conversion rate of −6%. Assuming a significance level of 0.05 and a power of 80%, the study plans to randomize 566 patients.

Estimated Dates for Completing Accrual and Presenting Results Patient recruitment will be completed by 2026, and follow-up will be completed by 2029 with presentation of data shortly thereafter. Two interim analyses are planned: one after the first 188 and the second after 376 randomized patients.

Trial Registration NCT05974995

INTRODUCTION

Endometrial cancer is the most common gynecologic cancer in high-income countries, and the second most common gynecologic cancer worldwide when both high- and low-income countries are considered.[1 2]

Incidence of endometrial cancer is expected to double in the next 10 years mainly due to the increasing prevalence of obesity, which accounts for approximately 40% of women, with severe obesity (body mass index (BMI)>40 kg/m^2) reaching 12%.[3]

According to the most recent guidelines, the standard procedure for uterine-confined disease is total hysterectomy with bilateral salpingo-oophorectomy and lymph node staging.[4] Two randomized prospective studies comparing minimally invasive with open surgeries proved laparoscopic surgical staging to be feasible in terms of short-term outcomes and equivalent in disease-free survival with no difference in overall survival. More recently, pooled analyses of randomized prospective studies and multiple retrospective and prospective studies support this result.[5 6] Thus, currently the accepted surgical approach for early-stage endometrial cancer is minimally invasive surgery. Notably, nearly 65% of patients with endometrial cancer who undergo primary hysterectomy have concurrent obesity (BMI 30–40 kg/m^2; 35–40%) or morbid obesity (BMI>40 kg/m^2; 25–30%), so the minimally invasive approach may be underused or unsuccessful in this group of patients with obesity because of technical challenges, limited exposure, and cardiopulmonary compromise while in the Trendelenburg position.

Previous studies analyzed the laparoscopic approach in patients with obesity. The Gynecologic Oncology Group LAP2 trial showed that the odds of

conversion to laparotomy during laparoscopic staging increased significantly with each unit increase in BMI. Conversion was usually performed when an adequate surgical staging could not be completed. The conversion rate in patients with normal BMI was 17.5% and increased to 26.5% in the group with BMI between 30 and 35 kg/m^2, and further increased to 57% in the group with BMI above 40 kg/m^2.[5] In 2015, Uccella et al proved that laparoscopy is superior to open surgery even in cases of morbid obesity with faster recovery and a higher likelihood of retroperitoneal staging compared with morbidly obese patients who underwent laparotomy.[7] Sentinel lymph node staging, a practice proven valid and accepted by international guidelines,[8 9] may reduce the high conversion rates described in the previously mentioned studies.

Retrospective studies show that robotic surgery is not inferior to other approaches and may have advantages when compared with laparoscopy in obese patients.[10 11] Cusimano et al published a systematic review and meta-analysis aiming to evaluate rates of conversion to laparotomy with laparoscopy or robotic surgery specifically in patients with endometrial cancer and BMI>30 kg/m^2.[12] They included 51 observational studies with a total of 10 800 patients overall and found that although the conversion rate for patients with BMI>30 kg/m^2 was comparable between laparoscopy and robotic surgery, the proportion of patients with BMI>40 kg/m^2 who experienced conversion were higher with laparoscopy compared with robotic surgery. Different reasons were described for conversion including organ or vessel injury, uterine size, advanced or metastatic disease, inadequate exposure because of adhesions or visceral adiposity, and anesthesiologic indications.[12]

Only two randomized controlled trials compared "conventional" laparoscopic surgery with robotic-assisted laparoscopic surgery.[13 14] Mäenpää et al randomized 101 patients with endometrial cancer to hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy either by robotic-assisted laparoscopic surgery or by traditional laparoscopy. They concluded that robotic-assisted laparoscopic surgery was faster than traditional laparoscopy. Also, the total time spent in the operation room was shorter in the robotic surgery group and all conversions to laparotomy occurred in the traditional laparoscopy group (five conversions to laparotomy in the laparoscopic surgery group vs none in the robotic surgery group). However, it should be noted that the average BMI of both groups was 29 kg/m^2.[13] ROBOGYN-1004 was a multicenter, phase III, superiority randomized trial that compared robot-assisted laparoscopy and traditional laparoscopy in patients with gynecologic cancer requiring minimally invasive surgery. They randomized 385 patients and the primary endpoint was the incidence of severe peri-operative morbidity. The investigators found robotic-assisted laparoscopy not superior to laparoscopy in terms of incidence of severe peri-operative morbidity, and they also observed no difference in the conversion rate to open surgery. However, robotic-assisted surgery was associated with a significantly longer operating time compared with laparoscopy. Again, the majority of patients recruited in the study were not obese (median BMI 26 kg/m^2).[14]

Robust data to help choose the most appropriate surgical technique in morbidly obese patients with endometrial cancer is missing, particularly in the era of sentinel lymph node.[15] This context strongly suggests that a clinical trial comparing the conversion rates between conventional laparoscopy and robotic assistance performed by surgeons equally proficient in both approaches may provide a response to a question for which high-level evidence is lacking. We hypothesize that robot-assisted laparoscopic surgery is superior to standard laparoscopy in terms of conversion rate and is associated with less morbidity, shorter surgical duration, better ergonomy, and superior patient-reported quality of life.

METHODS

Trial Design

The RObese trial is a prospective, international, multi-institutional, open-label, randomized controlled trial. The trial coordinator center is Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy. To date 10 sites from across Europe are expected to participate in the RObese trial. Obese women with early-stage endometrioid endometrial carcinoma will be evaluated and if they meet the inclusion criteria they will be subsequently randomized to either laparoscopic surgery or robot-assisted surgery (Figure 1). According to the most recent international guidelines, patients will undergo total hysterectomy with bilateral salpingo-oophorectomy and lymph node staging according to the Memorial Sloan Kettering Cancer Center algorithm.[16] The use of intrauterine manipulators is not allowed; closure of the cervical external orifice with a suture is recommended but not mandatory.

Surgery duration will be recorded. Operator ergonomics will be assessed using the Rapid Upper Limb Assessment (RULA), a risk assessment tool that calculates the risk of musculoskeletal loading within the upper limbs and neck. Intra-operative and post-operative complications will be recorded and classified according to the Clavien–Dindo nomenclature.[17] Patient-reported outcomes like quality of life will be evaluated at baseline (before surgery), at 1 and 4 weeks (early), and at 3 and 6 months (late) after surgery, using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire.

All data will be prospectively reported to an electronic database (RedCap platform) managed by the trial coordinator center.

Participants

The RObese trial will involve patients up to 85 years of age with morbid obesity with histological diagnosis of stage I endometrial endometrioid carcinoma according to the 2009 Federation of Gynecology and Obstetrics (FIGO) classification. Detailed inclusion and exclusion criteria are summarized in Table 1.

Endpoints

The RObese trial aims to compare the effectiveness of robot-assisted laparoscopic surgery with standard laparoscopy. The primary endpoint is the conversion rate to laparotomy, defined as the number of surgical procedures needing a conversion over the total number of surgical procedures in the two arms. Secondary endpoints include duration of surgery, peri-operative complications, surgeon ergonomics, disease-free survival, overall survival, and patient-reported quality of life.

Randomization

After verification of eligibility criteria and signed informed written consent, patients will be randomized to either robot-assisted surgery or laparoscopic surgery by equal allocation. The trial coordinator center will make available to satellite centers a variable permuted block randomization list. Randomization will be

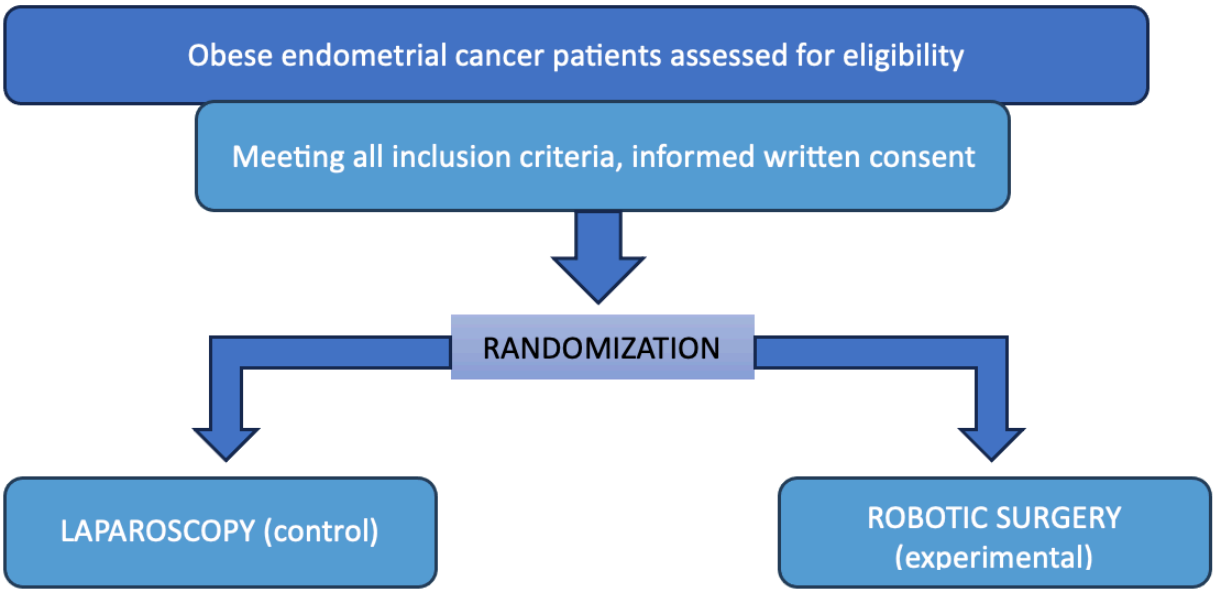

Figure 1 Study scheme of the RObese trial.

performed by entering the patient on a web-based instrument in the data collection database (RedCap).

Participating Centers and Surgeons

All surgeons participating in the RObese trial must have previous experience of at least 20 hysterectomies and lymph node assessment for endometrial cancer using both minimally invasive approaches and a congruent annual caseload.[18] It is at the discretion of the coordinating investigators to select individual surgeons to participate in the trial.

Sample Size and Statistical Methods

RObese is a superiority trial with the clinical superiority threshold defined as a difference in conversion rate of −6% between laparoscopic surgery and robot-assisted surgery. Assuming a conversion rate of 10% with the laparoscopic approach, a significance level of 0.05, and a power of 80% we will need to randomize 566 patients to detect an absolute difference in conversion rate of 6% (ie, conversion rate for laparoscopic surgery 10% vs conversion rate with robotic surgery 4%).

Two interim analyses based on sequential group approach are planned, one after the first 188 and the second after 376 randomized patients; the significance level to stop the trial for efficacy will be $p<0.0002$ and $p<0.012$ at the time of the first and second analysis, respectively. If the two interim analyses do not allow for an early stopping, the final analysis will be conducted at a significance level of 0.046.

As a general approach, descriptive summaries will be presented for the variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, maximum and interquartile range. Deviation from normality assumptions will be evaluated using the Shapiro–Wilks test. Categorical variables will be summarized using absolute frequency counts and percentages. All demographic and baseline clinical characteristics will be tabulated for each arm.

All randomized patients will be considered for the primary analysis. A sensitivity analysis will be performed on the population with no deviation from protocol. Secondary endpoints will be evaluated at the time of final analysis unless the study stops early due to an interim analysis; in this case secondary outcomes will be evaluated on that cohort.

Survival curves will be described according to the Kaplan–Meier product-limit method. Data will be also presented as medians, 95% confidence intervals of the median, and point estimates at 6-month intervals. The two groups will be compared by unstratified log-rank test. Hazard ratios will be estimated using the Cox proportional hazard model and reported with their 95% confidence intervals. IBM-SPSS v.28.0 statistical software and R v. 4.2.0 (CRAN; R Core, 2022, Vienna, Austria) will be used for analysis.

Table 1 Key eligibility criteria

Key eligibility criteria	
Inclusion criteria	BMI≥30 kg/m^2
	Age >18 years
	Histologically confirmed endometrioid endometrial cancer
	Clinical early stage (stage I)
	No contraindication for minimally invasive surgery
	American Society of Anesthesiologists (ASA) score <4
	Written informed consent
Exclusion criteria	Concomitant pelvic disease
	Age >85 years
	Any histology other than endometrioid
	Stage II-IV

DISCUSSION

As obesity rates are increasing worldwide, the incidence of endometrial cancer is also rising. Gynecologic oncologists are therefore increasingly required to deal with patients who represent a challenge from a surgical and peri-operative management standpoint in addition to anesthesia concerns. Minimally invasive surgery is currently universally recommended as the preferred approach for the surgical management and staging of endometrial cancer. Given the challenges associated with conventional laparoscopy in patients with obesity, robotic surgery is increasingly being used as an alternative, although in the absence of a solid literature evidence to justify its cost. In an era of staging of endometrial cancer limited to sentinel nodes, and consequently of de-escalation of systematic staging procedures, particularly aortic nodes dissection, the surgical management of endometrial cancer has been substantially simplified, raising the question of cost-effectiveness of robotic assistance.

Some features of robotic surgery such as better articulation of instruments, three-dimensional vision, and greater force applicable by robotic arms in supporting the weight of the abdominal wall may facilitate the completion of hysterectomy by a minimally invasive approach and even facilitate ventilation by allowing for reduced intraperitoneal/intrathoracic pressures. However, robotic surgery also results in increased costs per procedure. In an era of increasing attention to resource allocation in medicine, robotic surgery may be justified if clinical benefits over conventional laparoscopy can be demonstrated in this specific population.

Previous studies demonstrated that the minimally invasive approach for endometrial cancer is feasible for obese women but no randomized studies have compared laparoscopic surgery versus robotic-assisted surgery in morbidly obese patients. By identifying and highlighting differences in peri-operative and oncologic outcomes we hope to provide robust data to guide clinical practice in the years to come.

Evidence of clinical benefit for robotic surgery in patients with obesity would justify the additional resources required for this approach and may thus improve the adoption of minimally invasive surgery for this population.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Policlinico Agostino Gemelli IRCCS Ethics Commitee. Participants gave informed consent to participate in the study before taking part.

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