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)

SPONSOR: Fondazione Policlinico Universitario A. Gemelli IRCCS

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SUMMARY

Background: Endometrial cancer is the fourth cancer in women, the most common gynecologic cancer in high-income countries and the second most common gynecologic cancer worldwide. [1-2]

The high incidence of endometrial cancer is associated with several risk factors, but the growing prevalence of obesity has been identified as one of the majors. [3] Many patients with endometrial cancer are obese and have clinically relevant coexisting conditions [4] that negatively affects anesthesiological parameters and surgical performance when patients undergo surgery, thus potentially increasing the risk of peri-operative complications.

For patients presenting at early-stage disease the standard procedure is total hysterectomy with bilateral salpingo-oophorectomy and lymph nodal staging. Prospective and retrospective studies demonstrate that compared to systemic lymphadenectomy, sentinel lymph node mapping have high accuracy in detecting nodal metastases [5], and together with ultrastaging may increase the detection of lymph node metastasis with low false-negative rates in patients with apparent uterine-confined disease [6]. Also, recent evidence proved sentinel lymph node biopsy to be a feasible and safe alternative to lymphadenectomy in high-risk endometrial cancer [7].

Many randomized prospective studies proved laparoscopic surgical staging to be feasible in terms of short-term outcomes, equivalent in disease-free survival and no different in overall survival, thus the current surgical approach is minimally invasive [8-9]. Also, innovative surgical approaches such as robotic surgery have been exploited showing equivalent oncologic outcomes when compared to traditional laparoscopic surgery [10].

In 2015, Uccella et al. proved that laparoscopy is superior to open surgery even in case of morbid obesity. Particularly, minimally invasive surgery has been shown to have faster recovery and a higher likelihood of retroperitoneal staging in morbid obese patients, even if the number of women who received lymphadenectomy was found to be stable up to class II of obesity and then dramatically decreased to 30% for BMI>40. Similarly, the number of lymph nodes removed (when lymphadenectomy was accomplished), decreased significantly in class III obesity. However, the removal of lymph nodes can be less relevant in the era of sentinel lymph node. Once, the completing of lymphadenectomy could imply the need of conversion [11]. In fact, 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, but the reason for conversion was mainly when an adequate surgical staging cannot be completed.

In many retrospective studies robotic surgery has been shown to have advantages when compared to laparoscopy in obese patients [12-13]. 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 >30Kg/m^2: they included 51 observational studies with a total of 10,800 patients overall and found out that although the conversion rate for patients with BMI>30 Kg/m^2 is comparable between laparoscopy and robotic surgery, the proportion of patients with BMI >40 kg/m2 who experienced conversion seems to be higher in laparoscopy compared with robotic. Different reasons were described for conversion: organ/vessel injury, uterine size, advanced/ metastatic disease, inadequate exposure because of adhesions or visceral adiposity, anesthesiologic indications.

In conclusion, data across literature [14-15] suggest that robotic surgery may offer benefit specifically in patient with morbid obesity, but to date no randomized trials have been conducted to confirm these observations. Furthermore, conclusive data are needed to evaluate length of hospitalization, intraoperative and postoperative complications, adherence to the MSKCC nodal staging algorithm, and oncological outcomes in this group of patients.

Robust data in morbidly obese endometrial cancer patients to choose the most appropriate surgical technique are missing, particularly in the era of sentinel lymph node. Moreover, conversion to laparotomy in the previous study occurred to achieve a complete surgical staging with lymphadenectomy. Thus, we expect to have a lower conversion rate in our study.

Rationale: The rationale of the study is to find the most appropriate minimally invasive surgical approach in morbidly obese patients with endometrial carcinoma

Objectives:

Primary objective: To evaluate conversion rate to laparotomy with robotic surgery vs laparoscopic surgery (laparoscopic surgery referent group)

Secondary objectives:

- To evaluate difference in overall duration of surgery
- To evaluate difference in perioperative complications
- To evaluate the adherence to sentinel lymph node MSKCC algorithm
- To compare ergonomics of the two different surgical approach

- To compare quality of life (QoL) at baseline, 1 and 4 weeks (early), and 3 and 6 months (late) after surgery, using the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire
- To assess adherence to ESGO surgical Quality Index (QI, rate of uterine rupture)
- To evaluate difference in overall survival and disease-free survival

Primary end point: the number of surgical procedures that need a conversion over the total number of surgical procedures in the two arms.

Secondary end points:

- Duration in minutes of surgery
- Number of patients with at least one perioperative complications measured by Clavien Dindo
- To evaluate the ergonomics through the Rapid Upper Limb Assessment (RULA) assessment tool
- Disease-Free Survival (DFS) defined as the time between randomization and the first detection of relapse or death, whichever event occurs first; for patients without events DFS will be censored at the date of last follow-up
- Overall Survival (OS) defined as the time between randomization and death for any cause; for alive patients OS will be censored at the date of last follow-up

Study Design: Randomized Controlled Multicentric Superiority trial

Major Inclusion/Exclusion Criteria:

Inclusion criteria:

- BMI >30
- Age ≥ 18 and ≤ 75 years old
- Histologically confirmed endometrioid endometrial cancer
- Clinical early stage (stage I)
- No contraindication for minimally invasive surgery
- ASA < 4
- Written informed consent.

Exclusion criteria:

- High probability of laparotomy related to uterine volume (US estimated weight >250 g)
- Concomitant pelvic disease, or anatomical characteristics of the patient
- (Use of uterine manipulator)
- Age >75 years

Surgery requirements: trained surgeons (> 20 procedures for endometrial cancer in obese patients) in both surgical techniques

Preooperative workup:

- **MRI or CT scan** with imaging of aortic area and/or PET-CT to exclude patients with a presumed stage >2 disease
- **Pelvic US scan** to evaluate uterine volume

METHODS

Overall study design and flow chart:

Patients fulfilling inclusion criteria will be prospectively enrolled in the study and randomized to undergo either laparoscopic surgery or robotic-assisted surgery at Fondazione Policlinico Universitario A. Gemelli (FPG, Rome, Italy), and in the other satellite Centers.

All patients will receive a total hysterectomy with bilateral salpingo-oophorectomy and a lymph nodal surgical staging according to MSKCC algorithm: both hemipelvis will be individually evaluated, in case of no mapping on a hemipelvis, a site-specific pelvic, common iliac, and interiliac lymph node dissection (LND) will be performed and any suspicious or enlarged lymph nodes will be resected [16].

If total hysterectomy cannot be performed, or the uterus cannot be removed without the risk of rupture, or lymph nodal staging cannot be successfully achieved, the surgery will be converted to laparotomy. The conversion will not be judged on the base of frail o morbidly obese patients with significant risk of major postoperative complications according to surgeon and anesthesiologist judgment.

Sample size:

Assuming from data of literature a conversion rate of 10% with the laparoscopic approach, a significance level of 0.05 and a power of 80% we need to randomize 566 patients to detect an absolute difference in conversion rate of -6% (i.e. conversion rate for laparoscopic surgery 10% versus conversion rate with robotic surgery 4%). The two-sided Z-test will be used to assess this difference.

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; an alpha spending function based on O'Brien-Fleming Analog was used to determine these figures.

Statistical Analysis

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 through the Shapiro-Wilks test. Categorical variables will be summarized using absolute frequency counts and percentages. All demographical 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.

The primary endpoint will be analysed using the Z-test for proportion according to the parameters described in the previous section. A 95% confidence interval of difference in conversion rate between the two arms will be calculated.

Secondary endpoints will be reported with their 95% confidence analysis and P values will be nominal. Incidence of complications between the two arms will be compared with the chi square test or the Fisher Exact test, as appropriate. Differences in duration of surgery and evaluation of ergonomics through the RULA assessment tool will be assessed with the

Student's t-test or the Mann-Whitney test according to the deviation from normality assumptions.

Regarding quality of life the pattern of missing data will be analysed under different frames: rate of patients completing baseline assessments and the assessments at designated time points over the total number of randomized patients, rate of patients completing assessments at designated time points over the total number completing assessment at baseline. A generalized linear mixed model will be implemented to study the FACT-G items pattern.

Survival curves will be described according to the Kaplan-Meier product-limit method. Data will be also presented as median, 95% confidence interval of the median and point estimates at 6-month intervals. The two groups will be compared by unstratified log rank test.

Hazard ratio will be estimated with 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.

Estimated Study Duration: 36 months for the enrollment and 36 months for the follow-up.

Data collection and management:

All patients will be adequately informed and inserted in the study only after having read and signed an informed consent. Patients Health information (PHI) (name, medical record number, birthdate, sex, race, height, weight, medical and surgical history and dates of

diagnosis, laboratory and imaging test results, pathology reports, medication lists, allergies, clinic, hospital notes, follow up information, questionaries) will be prospectively recorded. The information obtained will be limited to the least amount required to accomplish the objectives of the research study. All PHI will be recorded prospectively using a database (REDCAP) and only accessible by the PI and study team.

Publication Policy

It is intended that after completion of the study, the data are to be submitted for publication in a scientific journal and/or for reporting at a scientific meeting. Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors).

ETHICAL CONSIDERATIONS:

All patients will receive complete surgical staging according to guidelines and there is no indication in guidelines to prefer robotic or laparoscopic approach. This study will be conducted in accordance with the protocol, the Fondazione Policlinico A. Gemelli Hospital Ethical Committee Approval, all applicable regulatory requirements, and the current guidelines of Good Clinical Practice (GCP). Compliance with GCP provides public assurance that the rights, safety, and well-being of study patients are protected consistent with the principles that have their origin in the Declaration of Helsinki. The Principal Investigator or his delegates agrees, when signing the protocol, to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

CONCLUSIONS:

Previous study clearly indicated that minimally invasive approach for endometrial cancer is feasible also for obese women but still no randomized studies compared laparoscopic surgery versus robotic-assisted surgery in morbidly obese patients with endometrial cancer. Our study aims to evaluate differences between the two approaches and offer evidence for better tailoring treatment in the future.

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