STUDY DOCUMENT

Official Title: COMPARISON OF SUPERFICIAL-ONLY INDOCYANINE GREEN INJECTION VERSUS THE COMBINED TECHNIQUE FOR SENTINEL LYMPH NODE MAPPING IN PATIENTS WITH ENDOMETRIAL CANCER: A RANDOMIZED CLINICAL TRIAL

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Abstract (English text already present in the original protocol)

Introduction: Endometrial cancer is the most common gynecologic malignancy in high-income countries and remains a major contributor to cancer-related morbidity among women worldwide. Although most cases are diagnosed at an early stage due to abnormal uterine bleeding, accurate nodal staging remains essential for prognostic stratification and adjuvant treatment planning. Historically, systematic pelvic and para-aortic lymphadenectomy was incorporated into surgical staging; however, multiple studies have demonstrated substantial procedure-related morbidity without a consistent survival benefit in patients with uterine-confined disease. Consequently, sentinel lymph node (SLN) mapping has become the preferred nodal assessment strategy in appropriately selected patients with apparent early-stage endometrial cancer. Indocyanine green (ICG), combined with near-infrared fluorescence imaging, is currently considered the tracer of choice because of its superior overall and bilateral detection rates. Despite its widespread adoption, significant variations in cervical injection techniques persist, particularly regarding injection depth, limiting procedural standardization and comparability across studies. Problem: The absence of prospective randomized evidence comparing different cervical ICG injection depths represents an important knowledge gap in SLN mapping for endometrial cancer. Suboptimal bilateral SLN detection may result in side-specific completion lymphadenectomy, increasing operative complexity and surgical morbidity while potentially influencing adjuvant treatment decisions. Establishing the optimal injection technique may improve mapping performance and facilitate broader procedural standardization. Objective: To determine whether exclusive superficial cervical injection of ICG is non-inferior to combined superficial and deep cervical injection for SLN mapping in patients with apparent FIGO stage I endometrial cancer, by comparing bilateral SLN detection rates, technical performance metrics, surgical outcomes, and long-term oncologic outcomes. Methods: This is a prospective, randomized, parallel-group, non-inferiority clinical trial. Participants will be randomized in a 1:1 ratio to undergo either exclusive superficial cervical injection of ICG (1 mL total) or combined superficial (1 mL) and deep cervical injection (1 mL).

Randomization will be stratified according to body mass index (BMI) categories. Consecutive women aged 18 years or older with histologically confirmed apparent FIGO stage I endometrial carcinoma undergoing minimally invasive surgical staging (laparoscopic or robotic approach) at Barretos Cancer Hospital will be eligible for enrollment after providing written informed consent. SLN mapping will be performed using near-infrared fluorescence imaging. Intraoperative variables will include time to visualization of the first SLN, total number of SLNs identified, mapping laterality, unilateral and bilateral detection rates, need for reinjection, and requirement for side-specific completion lymphadenectomy according to institutional SLN mapping algorithms. Clinical, surgical, pathological, and follow-up data will be prospectively collected and managed using the REDCap® electronic data capture platform, with periodic monitoring and quality-control audits. The primary endpoint will be the bilateral SLN detection rate. Secondary endpoints will include overall SLN detection rate, mean number of SLNs identified, time to SLN visualization, need for completion lymphadenectomy, pathological nodal status (isolated tumor cells, micrometastases, and macrometastases), concordance with final surgical staging, ICG-related adverse events, cervical injection-site complications, and retroperitoneal dye extravasation. Pelvic and para-aortic nodal recurrence rates during a five-year follow-up period will also be evaluated. Diagnostic performance analyses, including sensitivity, specificity, negative predictive value, and false-negative rate, will be performed for SLN mapping. The primary analysis will follow the intention-to-treat principle, with a complementary per-protocol analysis conducted for non-inferiority assessment. Between-group comparisons will be performed using the chi-square test or Fisher's exact test for categorical variables and Student's t-test or Mann–Whitney U test for continuous variables, as appropriate. Multivariable logistic regression models will be used to identify factors independently associated with successful bilateral SLN detection. Progression-free survival (PFS) and overall survival (OS) will be estimated using the Kaplan–Meier method and compared using the log-rank test. Multivariable Cox proportional hazards models will be used to evaluate survival outcomes. The sample size calculation was based on a non-inferiority design using an anticipated bilateral detection rate of 52% and a predefined non-inferiority margin of 7%. A total of 196 evaluable patients were required to provide adequate statistical power. Assuming a 10% rate of attrition, protocol deviations, or incomplete data, the final target sample size was increased to 216 participants. Expected Results: We hypothesize that exclusive superficial cervical injection of ICG will demonstrate non-inferiority compared with the combined superficial and deep injection technique regarding bilateral SLN detection. Furthermore, the superficial-only approach is expected to maintain staging accuracy while reducing technical artifacts associated with deep cervical injection, including dye extravasation, cervical bleeding, and tissue distortion. Confirmation of this hypothesis may support simplification and standardization of the SLN mapping procedure, reduce the need for completion lymphadenectomy, decrease surgical morbidity, and provide high-level prospective evidence to inform future guideline recommendations and optimize surgical staging practices in endometrial cancer.

Keywords: Endometrial cancer; Sentinel lymph node; ICG; Near-infrared fluorescence imaging; Injection depth; Lymph node staging; Bilateral detection; Lymphadenectomy; Prospective cohort; Surgical outcomes; Survival.

2. Hypothesis

Superficial-only cervical injection of indocyanine green (ICG) is hypothesized to be noninferior to combined superficial and deep injection with respect to bilateral sentinel lymph node (SLN) detection in patients with endometrial cancer. Superficial tracer deposition may adequately access the relevant lymphatic drainage pathways while reducing artifacts potentially associated with deep injection, such as extravasation, local bleeding, excessive tissue staining, and reduced fluorescence contrast. The superficial-only strategy is therefore expected to preserve staging efficiency, reduce the need for completion lymphadenectomy, and potentially decrease surgical morbidity without compromising oncological outcomes during follow-up.

3. Rationale

Sentinel lymph node mapping represents an important advance in the surgical staging of endometrial cancer because it may reduce morbidity compared with systematic lymphadenectomy while maintaining diagnostic accuracy. However, cervical ICG injection protocols remain heterogeneous, particularly regarding injection depth. Although deep injection has a physiological rationale, it has not been conclusively established whether it is necessary to achieve adequate bilateral SLN detection. Demonstrating noninferiority of superficial-only injection could simplify the technique, reduce injection-related artifacts and complications, and provide prospective comparative evidence to support standardized surgical practice.

4. Objectives

General objective: To evaluate whether superficial-only cervical ICG injection is noninferior to the combined superficial and deep technique for SLN mapping in patients with endometrial cancer.

• Compare bilateral SLN detection between the two techniques and test the noninferiority hypothesis.

• Assess overall SLN identification and the mean number of SLNs identified per patient.

• Compare time from ICG injection to visualization of the first SLN.

• Evaluate tracer migration failure and the need for reinjection, including reinjection on the unmapped side.

• Compare the need for completion pelvic lymphadenectomy on an unmapped side.

• Assess macrometastases, micrometastases, and isolated tumor cells identified in SLNs.

• Investigate concordance between SLN status and definitive lymph node staging.

• Compare operative time, estimated blood loss, intraoperative and postoperative complications, and ICG extravasation or injection-related artifacts.

• Assess ICG-associated adverse events.

• Evaluate pelvic and para-aortic lymph node recurrence over five years.

• Identify clinical, anatomical, and tumor-related factors associated with bilateral SLN detection using multivariable analysis.

• Compare empty-packet rates between techniques.

5. Materials and Methods

5.1 Study design

This is a multicenter, open-label, parallel-group, phase II randomized noninferiority clinical trial. Participants will be randomized 1:1, stratified by body mass index (BMI), to superficial-only cervical ICG injection (experimental group; 1 mL) or combined superficial (1 mL) and deep (1 mL) cervical injection (control group). Eligible participants will have histologically confirmed apparent FIGO stage I endometrial cancer and undergo minimally invasive laparoscopic or robotic surgical staging with near-infrared fluorescence SLN mapping. The primary endpoint is the bilateral SLN detection rate. Clinical, procedural, and oncological outcomes will be assessed longitudinally.

5.2 Sample size

The original protocol uses an anticipated proportion of 52% (177/340), obtained from a previously published study, and the conventional formula for estimating a proportion in an infinite population. With a 95% confidence level and a 7% margin of error, it reports an initial sample size of 196 participants. After allowance for 10% loss to follow-up or inconsistent data, the target sample is 216 participants. This paragraph describes the calculation as reported in the source; it does not independently validate a noninferiority power calculation.

5.3 BMI stratification

BMI will be used as a stratification factor to balance potential influences on lymphatic tracer migration and pelvic anatomy. The proposed distribution among 216 participants is: BMI below 27, 54 participants (27 per group); BMI 27–40, 108 participants (54 per group); BMI above 40, 54 participants (27 per group).

5.4 Study population and eligibility

Participants will be women aged at least 18 years with histopathologically confirmed endometrial cancer treated by the Gynecologic Oncology services of Barretos Cancer Hospital at the Barretos, Jales, and Porto Velho units. Eligible patients must have presumed stage I disease, an indication for minimally invasive laparoscopic or robotic surgery and ICG-based SLN mapping, adequate clinical fitness for surgery, and written informed consent. Exclusion criteria include contraindication to ICG, history of iodine allergy, previous treatment for a gynecologic malignancy, prior pelvic radiotherapy, and absence of complete data for the planned analyses, as specified in the source.

5.5 Randomization

A centrally generated sequence in REDCap will allocate participants 1:1 after eligibility confirmation and written informed consent. Randomization will be stratified by BMI. Allocation will be controlled by a research-team member who is not directly responsible for performing the intervention, and the surgical team will be informed of the assigned technique. Owing to the nature of the intervention, the trial will not be blinded. Assigned intervention and actual procedure will be documented prospectively.

5.6 Patient management and follow-up

At baseline, demographic, clinical, imaging, and pathological variables will be collected, including age, self-reported race or ethnicity, weight, height, BMI, performance status, anemia, comorbidities, smoking, pathology diagnosis date, FIGO 2023 clinical stage, and preoperative imaging. During surgery, investigators will record injection technique and site, time to first SLN visualization, number and laterality of mapped nodes, bilateral or unilateral detection, reinjection, completion lymphadenectomy, operative duration, estimated blood loss, complications, and surgical conversion when applicable.

For oncological safety, participants in the experimental arm with an unmapped pelvic side will receive combined superficial and deep reinjection (1 mL in each plane) before a side-specific systematic pelvic lymphadenectomy is undertaken. These patients will remain in their randomized group for intention-to-treat analysis. Subsequent records will include pathological and molecular findings when available, adjuvant treatments, recurrence, toxicities, and vital status. Follow-up visits are planned every three months for the first two years, every six months during years three and four, and annually thereafter through year five, with a ±15-day scheduling window. The original protocol specifies that the follow-up clock begins after completion of oncological treatment.

5.7 ICG administration

An appropriately trained investigator will administer ICG intraoperatively immediately before lymphatic mapping. The cervix will be exposed under anesthesia with the patient in the gynecological position. ICG will be injected bilaterally at the conventional 3 and 9 o'clock cervical sites. Patients will receive the randomly allocated superficial-only or combined superficial/deep injection. After an appropriate interval for tracer migration, pelvic lymphatic channels and SLNs will be visualized by near-infrared fluorescence imaging. Investigators will record mapping outcomes, dye extravasation, cervical bleeding, excessive tissue impregnation, poor fluorescence interpretation, and reinjection as applicable.

5.8 Histopathological assessment

Surgical specimens, including SLNs, nodes from any completion lymphadenectomy, the uterus and other resected tissues, will undergo standardized institutional pathological examination. Formalin-fixed, paraffin-embedded material will be stained with hematoxylin and eosin. The primary tumor will be evaluated for histology, grade, myometrial invasion, lymphovascular space invasion, cervical and parametrial involvement, other organ involvement, and final pathological stage. SLNs will be assessed separately by site and laterality, with ultrastaging when appropriate. Additional sections and immunohistochemistry may be used for equivocal findings. Isolated tumor cells, micrometastases, and macrometastases will be individually documented.

5.9 Adverse events

Events potentially related to ICG and the surgical procedure will be monitored intraoperatively, postoperatively, and during follow-up. The record will include event type, timing, severity, management, and outcome. Events of special interest include ICG hypersensitivity, hemodynamic changes, injection-site bleeding, tracer extravasation, tissue staining artifacts, difficulty with fluorescence visualization, and reinjection. Adverse events will be graded using the applicable version of the Common Terminology Criteria for Adverse Events (CTCAE); surgical complication grading may also be used when appropriate.

5.10 Statistical analysis

The primary endpoint will be bilateral SLN detection, evaluated under the intention-to-treat principle with a complementary per-protocol analysis for noninferiority. Categorical endpoints will be compared using the chi-square or Fisher exact test, and continuous variables by Student t or Mann–Whitney U test as appropriate. Multivariable logistic regression will examine factors associated with bilateral detection. Progression-free and overall survival will be estimated using Kaplan–Meier analyses, compared by log-rank tests, and investigated with Cox proportional hazards models. The protocol also proposes diagnostic performance assessments and five-year nodal recurrence analyses. The definitive noninferiority margin and inferential decision rule require careful statistical confirmation before submission.

5.11–5.14 Ethics, safety oversight, follow-up, and funding (condensed)

Participation requires documented informed consent and approval from the relevant institutional ethics committee. Potentially serious or unexpected ICG-related adverse events, clinically unacceptable complication patterns, evidence of inferiority at an interim assessment when undertaken, major operational failures, and ethical or regulatory concerns may justify partial or complete suspension of the study. Any discontinuation will not compromise participants' indicated medical and oncological care. Follow-up will document disease status, recurrence patterns, adjuvant treatment, toxicity, progression-free survival and overall survival for up to five years. The project will use existing institutional surgical, imaging, pathological, and REDCap infrastructure at Barretos, Jales, and Porto Velho. The source estimates approximately BRL 1,200 for administrative and operational expenses and states that Barretos Cancer Hospital will sponsor the study without dedicated external

industry funding.

Editorial note regarding translation scope

The complete introduction, detailed ethics and safety sections, original tables and figure, schedule, bibliography, and appendices have not been translated or reproduced in full in this partial edition. The existing abstract was retained in English from the source. Statistical calculations, inconsistencies and eligibility language should be reviewed by the investigative team before institutional or journal submission.