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Fluorescent Indocyanine Green versus Technetium-99m and Blue Dye for Bilateral SENTinel Lymph Node Detection in Stage I–IIA Cervical Cancer (FluoreSENT): protocol for a non-inferiority study

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ABSTRACT

Introduction Nowadays, two predominant methods for detecting sentinel lymph nodes (SLNs) in cervical cancer are in use. The most conventional method is a combination of a radiotracer, technetium-99m (^{99m}Tc) and blue dye. More recently, another method for SLN mapping using indocyanine green (ICG) is becoming widely accepted. ICG is a fluorescent dye, visualised intraoperatively with near-infrared (NIR) fluorescence imaging, providing real-time visual navigation. The presumed advantages of ICG over ^{99m}Tc, that is, being cheaper, non-radioactive and logistically more attractive, are only valuable if its detection rate proves to be at least non-inferior. Before omitting the well-functioning and evidence-based combined approach of ^{99m}Tc and blue dye, we aim to provide prospective evidence on the non-inferiority of ICG with NIR fluorescence imaging.

Methods and analysis We initiated a prospective non-inferiority study with a paired comparison of both SLN methods in a single sample of 101 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA–IB2 or IIA1 cervical cancer receiving primary surgical treatment. All patients undergo SLN mapping with ICG and NIR fluorescence imaging in adjunct to mapping with ^{99m}Tc (including single photon emission computed tomography with X-ray computed tomography (SPECT/CT)) and blue dye. Surgeons start SLN detection with ICG while being blinded for the preoperative outcome of SPECT/CT to avoid biased detection with ICG. Primary endpoint of this study is bilateral SLN detection rate of both methods (ie, detection of at least one SLN in each hemipelvis). Since we compare strategies for SLN mapping that are already applied in current daily practice for different types of cancer, no additional risks or burdens are expected from these study procedures.

Ethics and dissemination The current study is approved by the Medical Ethics Research Committee Utrecht (reference number 21–014). Findings arising from this study will be disseminated in peer-reviewed journals, academic conferences and through patient organisations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ We perform a powered, prospective non-inferiority trial comparing the bilateral sentinel node detection with indocyanine green (ICG) versus the combination of radiotracer (including preoperative imaging) and blue dye in cervical cancer.

⇒ The Fluorescent Indocyanine Green versus Technetium-99m and Blue Dye for Bilateral SENTinel Lymph Node Detection in Stage I–IIA Cervical Cancer (FluoreSENT) study is designed for intrapatient endpoint comparison, which increases statistical power and—contrary to a randomised controlled trial—allows for a direct comparison of detection rate and sentinel lymph node (SLN) anatomical localisation of the different tracers.

⇒ In the presented design, surgeons are blinded for the outcome of the radiotracer when starting SLN detection with ICG.

⇒ A limitation of this study design is the lack of blinding for the outcome of blue dye, which is visible with the naked eye.

Trial registration number NL9011 and EudraCT 2020-005134-15.

INTRODUCTION

Lymph node status is the strongest prognostic factor of survival in patients with cervical cancer and influences therapeutic management,[1] highlighting the importance of nodal assessment. To assess nodal stage accurately and efficiently in patients with early-stage cervical cancer, sentinel lymph node (SLN) mapping has emerged and could play a fundamental role in reducing the need for full pelvic lymphadenectomy. International studies are under way to assess the

performance of SLN resection alone versus pelvic lymphadenectomy in cervical cancer treatment.[2 3] For SLN mapping to be considered reliable, adequate detection and resection are essential. Since the cervix is a midline organ and lymphatic drainage is conducted bilaterally, high bilateral detection rates (defined as the proportion of patients with at least one SLN detected in each hemipelvis) are crucial for reliable SLN mapping.[4]

For mapping the SLNs, the conventional combined approach of radiotracer technetium-99m nanocolloid (^{99m}Tc) and blue dye previously has been proven to yield superior bilateral detection rates compared with using one of these tracers alone.[4–9] The radiotracer ^{99m}Tc enables preoperative imaging with SPECT/CT, while blue dye is added during surgery to visualise lymph nodes and afferent lymphatic vessels. However, certain disadvantages exist. Use of ^{99m}Tc with SPECT/CT exposes patients to ionising radiation. Intraoperatively, use of ^{99m}Tc only gives acoustic feedback and, with conventional gamma probes, is unable to provide real-time visual guidance. The 'long' radiotracer protocol (ie, 1-day preoperative admission for SPECT/CT) can be logistically challenging (demanding a nuclear medicine unit with safety protocols for handling), time consuming, involving longer hospital stay and leading to higher patient burden. Also, ^{99m}Tc usage is costly, especially in combination with preoperative SPECT/CT. Although the combination with intraoperative use of blue dye is beneficial in terms of bilateral detection rate, in a subset of patients, blue dye is associated with allergic reactions that may be severe (around 0.6%).[9 10] Common adverse effects related to blue dye are localised swelling or pruritus (2%–4%), transient discolouration of skin and urine (>95%) and a decrease in pulse oximetry readings due to colorimetric interference.[11 12]

The aforementioned disadvantages contributed to the recent shift towards SLN mapping with indocyanine green (ICG).[13] ICG is a non-radioactive fluorescent dye that is visualised intraoperatively with near-infrared (NIR) fluorescence imaging, providing real-time visual navigation. Recently, the Food and Drug Administration approved ICG for the indication of lymphatic mapping in uterine and cervical cancers.[14] Compared with ^{99m}Tc, ICG is non-radioactive, cheaper and logistically more attractive. Compared with blue dye, ICG has a better tissue penetration and a lower allergy risk. Overall, the use of ICG may lead to less burden on the patient as its use enables shorter hospital admissions and injection under anaesthesia.[15–17] The feasibility of ICG has been demonstrated, and early reports showed ICG yields high SLN detection rates in patients with early-stage cervical cancer.[18–21] Limitations of ICG include costs of NIR fluorescence equipment and less guidance towards unexpected SLN positions because of the absence of preoperative imaging.[22] Research in prostate cancer therefore suggests that preoperative SLN mapping provided by SPECT/CT remains essential in guiding intraoperative SLN localisation.[23] Another pitfall is the tissue penetration of NIR fluorescence imaging of approximately 1 cm, meaning it can be detected through a centimetre of overlying tissue,[24] which is especially limiting in patients with a high body mass index (BMI).[25 26] Also, the small hydrodynamic diameter of the ICG molecule may result in rapid spreading towards second and third echelon nodes,[16] undesirably leading to higher number of removed (false) SLNs. Although clinically the shift towards ICG seems to be in progress, shifting to an easy-to-use technique is not justified without prior evidence of its clinical reliability and validity, wherein it performs at least as good as the current standard of care.

In both endometrial and cervical cancer, adequately powered prospective trials comparing ICG with the more conventional method of ^{99m}Tc and blue dye are lacking.[27–30] The surgical practice has changed rapidly towards ICG in absence of level A evidence on its diagnostic accuracy. The unexpected recent findings of the Laparoscopic Approach to Cervical Cancer (LACC) trial have again stressed the importance of compelling evidence before switching to a new surgical technique.[31] Regarding cervical cancer, a prospective study by Lührs *et al* compared ICG with intraoperatively administered ^{99m}Tc in 65 patients with cervical cancer, without adding blue dye and without performing preoperative SPECT/CT imaging. The researchers reported a significantly higher bilateral detection rate of ICG compared with ^{99m}Tc without any significant improvement by combining the two. The lack of preoperative imaging in this study possibly affected the bilateral detection rate of ^{99m}Tc negatively, which was low at 60%.[32] The Fluorescence Imaging for Lymphatic Mapping (FILM) trial, a randomised non-inferiority trial comparing ICG with blue dye for SLN mapping in predominantly endometrial cancer (n=169, 96%) though also cervical cancer (n=7, 4%), reported significantly higher SLN detection rates with ICG than with blue dye only.[30] Besides its limited applicability in cervical cancer, a second major limitation is the absence of a radiotracer, making a comparison between ICG and the conventional combined approach impossible. Regarding endometrial cancer, prospective studies on the accuracy of ICG report greatly varying bilateral detection rates, ranging from 52% to 82%.[27–29 33 34] Researchers of the Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy (FIRES) and Sentinel Lymph Node Biopsy vs Lymphadenectomy for Intermediate- and High-Grade Endometrial Cancer Staging (SENTOR) trials report a bilateral detection rate of ICG (52% and 78%, respectively) that is lower than the reported bilateral detection rate of ^{99m}Tc with blue dye in relatively large prospective studies (eg, 80.5% in the SENTICOL (Ganglion Sentinelle dans le Cancer du Col) study[7]).[27 29] Soliman *et al* prospectively studied the bilateral detection rate in patients with endometrial cancer injected with either ICG, blue dye or ^{99m}Tc with blue dye.[33] Interestingly, the bilateral detection rate appeared to be highest with ^{99m}Tc with blue dye (82% vs 52% with ICG only). However, as stated by the authors, the study was not powered to detect a difference in detection rates

between the methods (p=0.35). How *et al* compared the three tracers (blue dye, ICG and ^{99m}Tc) simultaneously in 100 patients with endometrial cancer undergoing SLN mapping.[34] They found no significant difference in the bilateral detection of ICG versus ^{99m}Tc (65% with ICG vs 71% with ^{99m}Tc, p=0.36). When they compared ICG to the combination of ^{99m}Tc and blue dye, the difference in bilateral detection rate increased in favour of the conventional method: 65% with ICG vs 75% with ^{99m}Tc with blue dye. Of note, their results showed that ^{99m}Tc was the only tracer that detected all metastatic SLNs, which substantiates that a reliable SLN procedure can impact the survival.

Retrospective cohort studies reporting on the comparison of ICG versus ^{99m}Tc combined with blue dye exist but are generally of insufficient quality, underpowered and potentially suffer from publication bias. After a systematic review and meta-analysis of the available literature comparing ICG with ^{99m}Tc and blue dye, we found that the pooled bilateral detection rate with ICG appeared to be significantly higher.[35] However, in adherence with the Grading of Recommendations, Assessment, Development, and Evaluation guidelines, the quality of evidence was too low to provide strong recommendations and directly omit the combined approach of a radiotracer and blue dye. In addition, all included studies reported a higher average number of identified SLNs when using ICG as a tracer, indicating these are not likely to be all SLNs but rather second echelon lymph nodes. Failing to excise the true SLN could result in missed lymph node metastases. Currently, in both systematic reviews and European guidelines on cervical cancer, no consensus on the use of tracer has been reached, and both methods of SLN detection have been approved.[35–37] Before omitting any well-functioning and evidence-based procedure (^{99m}Tc combined with blue dye), high-quality evidence on the performance of ICG in cervical cancer SLN mapping is needed. In the FILM trial by Frumovitz *et al*, it was stated: 'Although the combination of blue dye and radiocolloid might be better than blue dye alone and equivalent to indocyanine green in detecting sentinel nodes, no studies – either prospective or retrospective – have compared the combination of blue dye and radiocolloid with indocyanine green'.[30] With our study, we intend to perform the proposed prospective study comparing ICG with the combination of radiotracer and blue dye (including preoperative SPECT/CT) in patients with early-stage cervical cancer. The presumed benefits of ICG are only valuable if its detection rate proves to be at least non-inferior to ^{99m}Tc and blue dye.

METHODS AND ANALYSIS

Study design

The Fluorescent Indocyanine Green versus Technetium-99m and Blue Dye for Bilateral SENTinel Lymph Node Detection in Stage I–IIA Cervical Cancer study is initially designed as a prospective, multicentre, non-randomised, single-arm, cross-sectional study in which we compare two SLN methods in patients with early-stage cervical cancer undergoing primary surgical treatment (FIGO stage IA–IB2 or IIA1): ICG with NIR fluorescence imaging versus ^{99m}Tc (including preoperative SPECT/CT) and blue dye. The study started in July 2021 and is coordinated by the University Medical Centre Utrecht and monocentric in the rollout phase. We plan to expand this study in other Dutch tertiary referral centres to increase the accrual rate. The planned end date of this study is July 2024.

Given that the current bilateral detection rate using ^{99m}Tc combined with blue dye is already high (86% in own cohort) and the use of ICG has substantial benefits, a non-inferiority design is justified.[38] When non-inferiority is reached, a switch in standard care to ICG with NIR fluorescence imaging (ie, abandoning ^{99m}Tc and blue dye) is supported, which will reduce the physical burden on the patient and logistic and financial burden on the healthcare system. If the detection rate with ICG proves to be inferior to ^{99m}Tc with blue dye, the extra burden of the conventional method would be justified as, in the end, patients will benefit most from the highest achievable bilateral detection rate. It is important to note that this is not an equivalence trial. When SLN mapping with ICG produces a higher bilateral detection rate than SLN mapping with ^{99m}Tc and blue dye, this is not considered a negative study result, whereas this is clearly a convincing reason to change the current practice. We chose bilateral detection rate as the primary endpoint because bilateral detection of SLNs has been proven to decrease false-negative rate (FNR) and is thus considered to improve reliability and oncological safety.[4 39] This protocol has been developed in line with research protocol template of the Central Committee on Research Involving Human Subjects and the SPIRIT recommendations.[40]

Study population

The subjects will be drawn from a population of patients with histopathologically proven primary malignancy of the cervix uteri. Patients are eligible to participate if they are scheduled for a (robot-assisted) laparoscopic or open SLN procedure as part of the standard surgical treatment for FIGO stage IA1–IB2 or IIA cervical cancer (according to the FIGO 2018 guidelines[41]), aged ≥18 years and able to provide informed consent. Exclusion criteria are pregnancy or current breast feeding, renal insufficiency stage 3 or 4, prior allergic reaction to ICG, ^{99m}Tc or patent blue, and prior severe allergic reaction to iodine. Informed consent will be obtained before the start of any study activity.

Sample size

The sample size calculation was based on our own data and current literature. Data from our historical cohort showed a bilateral detection proportion of 86% (95% CI 80% to 91%) for SLN mapping with ^{99m}Tc and blue dye (Hoogendam *et al*[38]). The pooled proportion of bilateral detection rate of ICG was found to be between

89.4% and 91.5%, depending on how studies in the meta-analysis were handled (in preliminary analysis). Based on consensus discussion by clinicians in the study team and a comprehensive review of the literature, a non-inferiority margin of 0.05 was set. For assessing non-inferiority in paired proportions, the asymptomatic test statistic, which is the so-called Nam score test, or restricted maximum likelihood estimation-based test statistic was used.[42] The power and sample size was calculated in the statistical software package Power Analysis and Sample Size (PASS), verified for non-inferiority tests (one-sided) for two correlated proportions.[43] The calculations were checked by a statistician (power formula is provided in the PASS User's Guide[43]).

In conclusion, comparing a proportion (^{99m}Tc and blue dye at 0.86, ICG 0.89) in one sample with a non-inferiority margin of 0.05, with a type I error (α) set at 0.05, a type II error (β) set at 0.2 (power 1–β=0.8) and nuisance set at 0.12 (based on the proportion of discordant pairs), we require a sample size of 101 cases. The complete list of parameters used for the power calculation is provided in online supplemental appendix 1.

Investigational product

ICG is a fluorescent agent used for diagnostic purposes in adults and children with a benign safety profile. One of the diagnostic purposes is fluorescence imaging of lymph nodes and delineation of lymphatic vessels in the cervix and uterus in patients with solid tumours during lymphatic mapping. No therapeutic effects are expected. ICG (VERDYE 25 mg, Diagnostic Green GmbH, Germany) is registered for diagnostic purposes in adults under Dutch RVG number 31 052.

Allergic reactions and anaphylactic shocks due to ICG were reported in very rare (<0.01%) cases. In patients with renal insufficiency, the risk of anaphylactic shock appears to be higher. In very rare cases, spasms of the coronary arteries are described. Radioactive iodine uptake studies should not be performed for at least a week following the use of ICG. No other complications or potential risks of ICG are reported.[14]

Trial intervention

The flowchart in figure 1 presents a schematic overview of the study design. All subjects undergo an SLN procedure as part of the surgical treatment and receive ICG injection in adjunct to the current combined approach. Subjects will be preoperatively injected with ^{99m}Tc followed by a SPECT/CT 90–120 min post injection (according to current standard of care).[38] The surgeon (gynaecological oncologist) will not consult the SPECT/CT preoperatively (secured by automated logging of consultation). At the start of surgery, subjects are injected with 4 mL of ICG 1.25 mg/mL (study procedure) and 4 mL of blue dye (standard of care) under general anaesthesia; 1 mL of both tracers into each quadrant of the cervix (ie, at 3, 6, 9

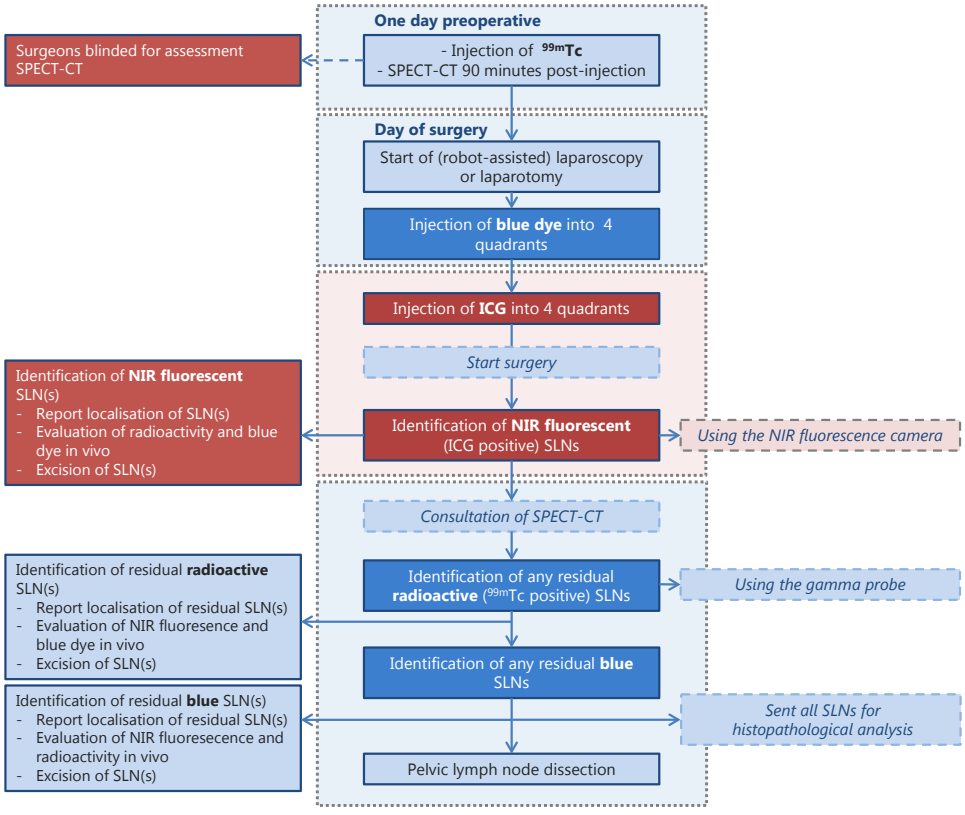

Figure 1 Flowchart of study procedures. Blue boxes represent the current standard of care; red boxes represent the study-specific procedures. ^{99m}Tc, technetium-99m nanocolloid; SPECT-CT, single photon emission computed tomography with X-ray computed tomography; blue dye, patent blue; ICG, indocyanine green; NIR, near-infrared; SLN(s), sentinel lymph node(s).

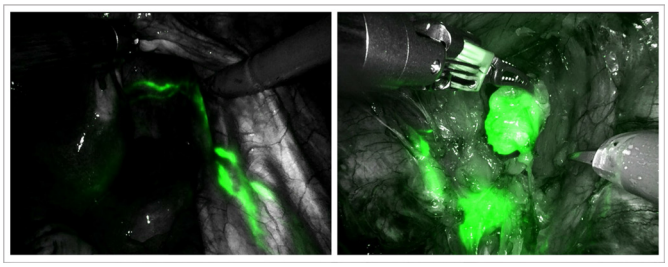

Figure 2 Fluorescence-guided surgery showing lymphatic vessels (left) and sentinel lymph node (right).

and 12 o'clock, following the internal protocol). During surgery, the SLNs will be first identified with NIR fluorescence light using FireFly fluorescent imaging system (Intuitive Surgical) in robotic surgery or a CE-marked NIR fluorescence platform applicable to laparoscopic or laparotomic surgery; in this light, NIR fluorescent nodes will light up green (figure 2). Localisation of each NIR fluorescent SLN will be reported. When the NIR fluorescent SLN(s) are identified, the gynaecological oncologist will check the SLN(s) for radioactivity with a gamma probe (either in vivo or ex vivo) and blue colour. When completed, the procedure is repeated in the contralateral hemipelvis. Results are reported as follows: of each SLN, the localisation is reported according to a standardised format (see online supplemental appendix 2) and it is stated if detected with NIR fluorescence (ICG), radioactivity (^{99m}Tc) and/or blue colour (blue dye). All SLNs identified are excised. After finishing this procedure bilaterally, the surgeon consults the SPECT/CT (time of deblinding is logged both automatically and manually) and reports whether radioactive node(s) on SPECT/CT correspond to the excised SLN(s). To prevent missing SLNs, the pelvic site will be checked for residual radioactive nodes and blue nodes and excised, if present. Residual radioactivity of the surgical site will be measured and deemed negative if background counts are less than 10% of the maximum SLN count.

Blue dye and ICG are injected sequentially, before entering the retroperitoneal space. Previous studies using a combined injection of patent blue and ICG experienced no clotting of the two dyes, both at macroscopic and microscopic levels.[34 44 45] To prevent from bias in detection of SLNs, injecting blue dye in a later stage of surgery—that is, after SLN mapping with ICG and NIR fluorescence is completed—has been explored. However, starting SLN mapping with ICG would result in anatomical structures and lymphatic vessels that have already been destructed. Because of the destructed lymph vessels, injecting blue dye in a later stage would underestimate the true benefit as the dye will not reach the lymph nodes. This intrapatient study design is thereby limited by the inability of blinding for the outcome of blue dye.

Except for injection of ICG and detection with NIR fluorescence imaging while blinded for the assessment of the SPECT/CT, the complete treatment is maintained according to the current standard of care. Intraoperative recordings and pictures can be made for retrospective tumour-to-background ratio analysis. All follow-up visits take place according to the national guidelines. There is no special follow-up required for subjects in this study. Subjects are asked to fill in the IN-PATSAT32 questionnaire postoperatively, developed by European Organisation for Research and Treatment of Cancer (EORTC), for assessing patients' perception of the quality of hospital-based care (not mandatory).

Outcomes

The primary outcome is bilateral detection rate of SLNs with ICG and NIR fluorescence imaging versus ^{99m}Tc (including preoperative SPECT/CT) and blue dye. SLN is defined as the first lymph node(s) of each hemipelvis to receive afferent lymphatic drainage from the primary cervical tumour, identified by either ICG, gamma radiation using ^{99m}Tc or blue dye. Bilateral detection is defined as the number of patients detected with at least one SLN in each hemipelvis.

Secondary outcomes include[1] overall (ie, at least unilateral) detection rate, sensitivity and FNR of ICG and ^{99m}Tc and blue dye, with pelvic lymph node dissection as the reference standard to confirm tumour-positive lymph nodes (part of current standard of care)[2]; correlation between NIR fluorescent, radioactive (both intraoperative and with SPECT/CT) and blue-stained SLNs in terms of anatomical location[3]; adverse events of ICG, ^{99m}Tc and blue dye[4]; time to complete SLN detection with ICG versus ^{99m}Tc and blue dye[5]; cost-effectiveness comparison (cost of procedure versus yielded bilateral detection rate) of ICG versus ^{99m}Tc and blue dye SLN detection[6]; surgical evaluation of NIR fluorescent imaging (usability) measured with two short questionnaires tailored for the surgeons; and[7] patient satisfaction with the oncological care and procedure measured with the validated EORTC IN-PATSAT32 questionnaire.

The basic clinical, surgical and histopathological parameters will be recorded, including age at diagnosis, BMI (in kg/m^2), history of abdominal surgery, American Society of Anaesthesiologists classification, FIGO stage (2018), type of procedure, tumour histology and size, lymph vascular space invasion, nodal count and status, parametrial involvement, vaginal involvement, positive resection margins and adjuvant or adjusted treatment (the latter due to intraoperative finding of positive lymph nodes). Subanalysis will evaluate if these parameters are possible confounders or effect modifiers.

Data collection and management

All measurements will be systematically recorded using an electronic clinical report form built in Castor Electronic Data Capture system. Data will be collected in coded form and monitored by data managers from the UMC Utrecht. Baseline characteristics are collected pseudonymously from the medical records in consultation with the data management department of the research centre(s). All study procedures at the research centre(s) are

monitored by an independent monitor during multiple visits according to a specified protocol.

The principal investigators at the research centre(s) bear responsibility for safe data handling. After the project is finished, data will be stored for 25 years according to the current Medical Research Involving Human Subjects Act (WMO). Handling of personal data will comply with the EU General Data Protection Regulation and the Dutch Act on Implementation of the General Data Protection Regulation.

Adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the intervention (SLN mapping with ICG and NIR fluorescence). All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. A serious adverse event (SAE) is any untoward medical occurrence or effect that occurs in the 48 hours following the SLN procedure. The sponsor will report the SAEs through the Dutch web portal ToetsingOnline to the accredited medical ethics research committee that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the SAEs.

Statistical analysis

We will perform a comparison (single sample) of two diagnostic modalities and aim to assess non-inferiority (note: not equivalence) of the ICG SLN mapping in terms of bilateral detection rate. Our analysis is based on previous literature on non-inferiority for paired binary data.[42] Statistical software programmes SPSS (version 26.0.0.1 or higher) and R will be used to perform the analyses. The measured primary endpoint is the proportion of bilateral SLN detection, which is tested in a paired setting. The null (H0) and alternative (H1) hypotheses for this non-inferiority study are as follows:

- H0: SLN mapping with ICG is inferior to SLN mapping with ^{99m}Tc and blue dye with respect to the proportion of bilaterally detected sentinel nodes.
- H1: SLN mapping with ICG is non-inferior to SLN mapping with ^{99m}Tc and blue dye with respect to the proportion of bilaterally detected sentinel nodes.

The analysis of all outcome data will be performed using intrapatient comparison (McNemars test). Categorical and continuous data will be presented in a quantitative way. The bilateral detection rates of ICG, ^{99m}Tc and blue dye are presented separately with corresponding 95% CIs. Categorical data will be analysed using the Fisher exact or χ^2, as appropriate. For continuous outcomes, t-test will be used in case of normally distributed data. If not normally distributed, Mann-Whitney U test will be performed. Besides 95% CIs, p values will be reported with a value of <0.05 considered significant.

In case of identified inconsistencies or missing data, additional source documents will be requested from the study site to resolve ongoing inconsistencies. If necessary, patients are called to resolve missing data. If missing data restrict further analysis, multiple imputation analyses will be conducted.

Patient and public involvement

Members of patient organisation Stichting Olijf were involved in the design of this study.

ETHICS AND DISSEMINATION

This current study was approved by institutional review board and Medical Research Ethics Committee Utrecht (number 21–014) in accordance with the Dutch WMO and other applicable Dutch and European guidelines, regulations and Acts. The study was registered in the Netherlands Trial Register. All subjects will have to sign and date written informed consent. No study activities will occur prior to obtaining consent. Subjects retain the right to withdraw at any point for any reason. See online supplemental appendix 3 for the approved version of the Dutch patient information and informed consent form for this study (in line with the model form provided by the Central Committee on Research Involving Human Subjects).

This study has been assessed as a low-risk study. ICG is given in adjunct to the current standard of care and subjects are not withheld of any type of standard treatment. Risks associated with participation can be considered negligible. Participating in this study will be associated with minor discomfort and might be beneficial for individuals, as mapping with ICG might result in higher SLN detection rates (based on previous literature). This study intends to improve oncological care and prognosis for all patients with early-stage cervical cancer.

We will ensure our findings and the acquired knowledge will be transferred to clinicians and researchers in the field. Findings arising from this study will be published at national and international conferences. The final manuscript will be submitted for publication to an open access peer-reviewed scientific journal. Both positive and negative trial results will be disclosed. Results will also be updated in the Netherlands Trial Register, which is the primary registry for the Netherlands and recognised and accepted by the WHO and ICMJE. Subjects and patients with cervical cancer will be informed about the study results by the newsletter and social media accounts of patient organisation Stichting Olijf.

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Competing interests RPZ is a proctor for robot-assisted surgery in gynaecological oncology on behalf of Intuitive Surgical.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods and analysis section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Medical Ethics Research Committee, Utrecht (reference number 21-014). The participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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