Gynecologic Oncology Reports 43 (2022) 101054

Contents lists available at ScienceDirect

Gynecologic Oncology Reports

journal homepage: www.elsevier.com/locate/gynor

Research Report

Technetium Tc 99m tilmanocept fails to detect sentinel lymph nodes in endometrial cancer

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A B S T R A C T

Background: Technetium Tc 99m tilmanocept is a synthetic radiotracer specifically designed for sentinel lymph node (SLN) mapping that has been FDA-approved in breast cancer, melanoma, and head and neck cancer. No published studies exist for the use of this radiotracer in endometrial cancer.
Objective: The primary objective was to determine the detection rate of bilateral SLNs in endometrial cancer with the concurrent use of technetium Tc 99m tilmanocept and ICG.
Methods: An open-label, single cohort, prospective feasibility study was conducted with participants receiving preoperative cervical injections of technetium Tc 99m tilmanocept followed by subsequent imaging and SPECT/CT. Intraoperative ICG injections were administered for all patients with near-infrared imaging used to visualize lymphatic vessels and nodes. A laparoscopic gamma counter was used to detect radioactive SLN intraoperatively.
Results: All six evaluated patients had FIGO grade 1 or 2 endometrioid histology. Stage IA/IB were in 33% and 66% of patients, respectively. Tilmanocept did not map any SLN in the first six patients but instead showed retention of the tracer in the cervical stroma, leading to study discontinuation for futility. ICG mapped bilateral SLN in all patients with the most common location being the external iliac region, followed by the obturator and common iliac areas. All patients had CD206 positive staining throughout the full wall thickness of ectocervix, transformation zone, endocervix, and lymphatic vessels. No patients experienced adverse events.
Conclusion: Technetium Tc 99m tilmanocept did not detect SLN in early stage endometrial cancers and is unlikely to improve bilateral detection rate compared to ICG alone. ICG remains a standard technique for SLN detection in low stage, low grade endometrial cancer.

1. Background

Endometrial cancer accounts for approximately 50% of all gynecologic malignancies in the United States (Siegel et al., 2020). The International Federation of Gynecology and Obstetrics (FIGO) revised endometrial cancer staging in 1988 to make it a surgical staging system, which includes complete pelvic lymphadenectomy (Mikuta, 1993). Despite the increased accuracy in staging, complete lymphadenectomy has not been shown in randomized trials to increase progression-free or overall survival (Panici et al., 2008; Kitchener, 2009). Additionally, complete lymphadenectomy carries the risk of increased morbidity, including lymphedema and nerve damage. To reduce this morbidity while maintaining prognostic information, the concept of sentinel lymph node (SLN) sampling has been introduced (Abu-Rustum et al., 2009; Holloway, 2017).

SLN evaluation has become standard of care in cutaneous melanoma and breast cancers, and is becoming increasingly utilized in gynecologic malignancies. In cervical cancer, SLN biopsy has been demonstrated to decrease morbidity without impacting disease-free survival in select patients. For vulvar cancer, large prospective studies have attested to the high sensitivity of SLN biopsy with ongoing research investigating the role of adjuvant therapy with positive SLNs. While the use of SLN injection and biopsy remains investigational in ovarian cancer, it is now widely accepted as the standard of care in select endometrial cancer patients with early stage disease (Chow, 2022).

Various tracers, including radioactive tracers and dyes, have been used to identify the sentinel lymph node and assess for tumor involvement, all with similar detection rates (Nagar, 2021). In a large, multicenter prospective trial, detection rates for SLNs in minimally invasive surgery for early stage endometrial cancer using indocyanine green (ICG) alone have been reported as 52 % bilaterally and 86 % overall (Rossi, 2017). Our own institutional data show detection rates using ICG

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https://doi.org/10.1016/j.gore.2022.101054
Received 26 July 2022; Accepted 27 July 2022
Available online 30 July 2022

of 69 % bilaterally and 88 % overall (Renz, 2019). If a SLN is detected, only the SLN is removed and a complete lymphadenectomy is avoided. If SLNs are not detected, current guidelines recommend a complete lymphadenectomy on the side where the SLN was not identified (Barlin, 2012).

2. Tracers for sentinel lymph node detection

Historically, SLN sampling was first described in the late 1970 s for penile cancer using the injection of radiocolloids (Cabanas, 1977). Radioactive tracers are filtered or non-filtered sulfur colloids, most commonly radiolabeled with technetium-99m (Tc 99m). The major advantage of radioactive tracers is deep tissue penetration and the ability to detect SLN locations preoperatively. Concerns regarding the use of radioactive colloids are (i) the non-specific and passive distribution of the tracer colloids throughout the lymphatic system by lymph flow and/or diffusion, which diminishes the retention of the tracer in the first draining lymph node and results in the leakage of radiotracers to subsequent lymph nodes; (ii) the need for preoperative injection and imaging, and (iii) the safe handling of a radioactive substance.

To simplify the intraoperative detection of SLNs, various vital dyes have been utilized, e.g. isosulfan blue 1 %, methylene blue 1 %, and patent blue 2.5 % sodium. Isosulfan blue is the only dye that has been FDA approved for SLN detection. Overall and bilateral detection rates in endometrial cancer have been reported at 63–78 % and 40–46 %, respectively (Tanner, 2015; Holloway, 2017; Sinno, 2014). Disadvantages of isosulfan blue are (i) the cost, (ii) risk of an anaphylactic reaction (1.1 %), and (iii) the comparably poor deep tissue penetration, especially of adipose tissue (Albo, 2001). There is evidence from breast cancer on the equivalence of methylene blue and isosulfan blue (Blessing, 2002), and reported overall and bilateral detection rate for methylene blue in robotic-assisted laparoscopic surgery in endometrial cancer are 86 % and 52 %, respectively (Desai, 2014). Methylene blue is less expensive and has a lower, but still significant, risk of allergic reactions. As in breast cancer and melanoma, combinations of vital dyes and radioactive tracer colloids have been used in endometrial cancer to improve the detection of SLN, with reported overall and bilateral detection rates of 90–97 % and 65–76 %, respectively (Ballester, 2011; Bats, 2013; Touhami, 2015).

Recently, indocyanine green (ICG) has emerged as useful imaging dye that requires a near-infrared camera for localization. One main advantage of a near-infrared fluorescent dye over a blue dye is the improved visibility through visceral fat. Overall and bilateral detection rates have been reported as 86–96 % and 52–88 %, respectively (Rossi, 2017; Tanner, 2015; Sinno, 2014; Jewell, 2014; Plante, 2015). Compared to blue dyes, allergic reactions are very rare with an estimated anaphylactic rate of 0.05 % as demonstrated in ophthalmic literature (Hope-Ross, 1994). Disadvantages of ICG are (i) the required special equipment, i.e. near-infrared camera and (ii) the dye dissemination, which is inherent to all non-specific radioactive and colored tracers. While not specific to ICG, there is potential for diminished retention in the first draining lymph nodes and the possibility of detecting lymph nodes subsequent in the lymph node chain.

3. Study agent - technetium Tc 99m tilmanocept

Technetium Tc 99m tilmanocept (brand name Lymphoseek) was first synthesized and described in 2001 by Vera et al. (Vera, 2001). In contrast to other dyes and tracers used in SLN detection, this synthetic radiotracer was specifically designed for SLN mapping and is the first FDA-approved receptor-targeted lymphatic mapping agent. The molecule consists of a dextran backbone and eight diethylenetriaminepentaacetic acid (DTPA) groups. The DTPA groups are used for the chelation of Tc 99m technetium. The dextran backbone is covalently bound to 55 mannose residues, which provide high receptor affinity to the mannose receptor CD206, commonly found on the surface of macrophages and dendritic cells. Technetium Tc 99m tilmanocept has a relatively small molecular size (MW = 16.7 kDa) and low dissociation constant (0.12 nmol/L), which ensures the effective uptake of the agent by the SLN as well as improved retention. As a result, there is lower distal lymph node accumulation than seen for the nonreceptor-targeted filtered Tc 99m-sulfur colloid (Baker, 2015). Technetium Tc 99m tilmanocept accumulates in fewer lymph nodes with higher specificity (Wallace, 2003).

The dextran backbone offers rapid injection site clearance and diffusion through lymph and blood vessels. By providing higher signal-to-noise ratio, technetium Tc 99m tilmanocept was designed to offer a better detection rate than an agent with slower clearance (Baker, 2015). Technetium Tc 99m tilmanocept clears the injection site within 10 min and accumulates in SLNs where it remains bound for up to 30 h.

While Technetium Tc 99m tilmanocept has been FDA-approved in breast cancer, melanoma, and head and neck cancer (FDA, Prescribing information on Lymphoseek., 2016), at the time of this trial no published studies exist for the use of technetium Tc 99m tilmanocept in endometrial cancer.

4. Rationale

Technetium Tc 99m tilmanocept was conceptualized to be added to the SLN algorithm for endometrial cancer in order to improve bilateral and overall SLN detection rates. Preoperative imaging using single photon emission computed tomography (SPECT/CT) would provide critical preoperative information about the location of SLNs, and aid in the detection of SLN in atypical locations such as the pre-sacral and *para*-aortic regions (Marcinow, 2013). A laparoscopic gamma counter would identify sentinel lymph nodes intraoperatively. By combining technetium Tc 99m tilmanocept and ICG, it was proposed that SLN detection rates would improve and surgical morbidity associated with a complete lymphadenectomy would decrease.

The primary objective of this trial was to determine the detection rate of bilateral SLNs with the concurrent use of technetium Tc 99m tilmanocept and ICG. Secondary objectives were 1) to determine the location and number of technetium Tc 99m tilmanocept-positive SLNs preoperatively by SPECT/CT imaging and intraoperatively by a laparoscopic handheld gamma detector; 2) to determine the location and number of ICG positive SLNs by intraoperative infrared fluorescent imaging; 3) to determine the concordance of technetium Tc 99m tilmanocept and ICG SLN detection; 4) to assess the safety of the concurrent use of technetium Tc 99m tilmanocept and ICG.

5. Methods

This study was an open-label, single cohort, prospective feasibility study to assess the detection rate of bilateral SLNs with concordant use of technetium Tc 99m tilmanocept and ICG in patients with endometrial cancer. Participants were required to have a histological diagnosis of endometrial cancer of any histology or grade that was confined to the uterus, to not have received any prior treatment for the endometrial cancer and to be a candidate for minimally invasive surgery. Excluded patients included those with clinical or radiological evidence of metastatic disease or a history of prior cervical conization procedure. Full inclusion and exclusion criteria are detailed in Supplementary Table 1. The study was approved by the Institutional Review Board and Cancer Institute Scientific Review Committee at the institute where it was conducted. The trial is registered on clinicaltrials.gov (NCT04511026).

Participants received cervical injections of technetium Tc 99m tilmanocept 0.125 mCi × 4 each at 3, 6, 9, and 12o'clock (or 0.5 mCi +/- 20 %) in the uterine cervix for same day surgery or 0.5 mCi × 4 each at 3, 6, 9 and 12o'clock (2.0 mCi +/- 20 %) for next day surgery 1–24 h prior to surgery. All the technetium Tc 99m tilmanocept and ICG injections were performed by a single operator using identical technique. Subsequent imaging was obtained preoperatively with immediate and delayed

static planar images with and without a transmission source, as well as SPECT/CT of the abdomen and pelvis for further characterization. These images were available for the surgeon to review prior to the start of surgery. Participants were observed in the nuclear medicine suite after injection for possible allergic reactions or other adverse events.

Intraoperatively following anesthesia induction, 0.5 mL of 0.5 mg/mL indocyanine green was injected into the four quadrants of the uterine cervix. Near-infrared imaging was used to visualize lymphatic vessels and lymph nodes. A handheld wireless laparoscopic gamma counter was used to detect radioactive SLN intraoperatively.

Participants were assessed postoperatively in the post-anesthesia care unit for possible adverse effects prior to discharge. They were re-assessed at their routine postoperative visit scheduled between 14 and 28 days following surgery. Visits were scheduled in person or via telemedicine based on patient preference, with physical examination and adverse event evaluation conducted remotely for those patients who opted for telemedicine appointments.

In addition to the clinical analysis above, formalin-fixed paraffin embedded (FFPE) blocks of cervical tissue were created for each patient postoperatively and CD206 staining was performed. CD206 is a mannose binding receptor protein located on many cell surfaces, including macrophages and dendritic cells. The mannose backbone of technetium Tc 99m tilmanocept has high affinity for CD206. Therefore, CD206 staining was used to signify localization of technetium Tc 99m tilmanocept (International Atomic Energy Agency, 2015; Wallace, 2013).

5.1. Statistical analysis

Descriptive statistics were used to analyze the primary and secondary outcomes, as summarized using frequencies and percentages.

To address the primary objective, a sample size of 30 patients was planned to receive concurrent administration of technetium Tc 99m tilmanocept and ICG. The bilateral detection rate using current techniques at our institution is approximately 69 %. Based on this, we would consider a bilateral detection rate of 80 % to be promising. With 30 participants and assuming a true bilateral detection rate of 80 %, the probability of correctly concluding that our approach has an acceptable bilateral detection rate (i.e. 24 patients being detected with bilateral SLNs) is 61 %. The probability of incorrectly concluding this is low at 13 %. The exact 95 % confidence interval for the assumed bilateral detection rate of 80 % is 61 % to 92 %.

6. Results

Technetium Tc 99m tilmanocept failed to identify any SLN with preoperative SPECT/CT imaging or by intraoperative gamma probe in the first six patients enrolled on trial. Instead, technetium Tc 99m tilmanocept was found in high concentration in the cervix on preoperative SPECT/CT imaging (Fig. 1). The concurrent use of ICG resulted in successful bilateral mapping in all six patients. Due to the absence of detection of SLNs by technetium Tc 99m tilmanocept as well as bilateral SLN detection using ICG alone in the first six patients, a committee consisting of the authors and supported by our institution's cancer research group decided to discontinue the study due to futility after a review of preliminary results.

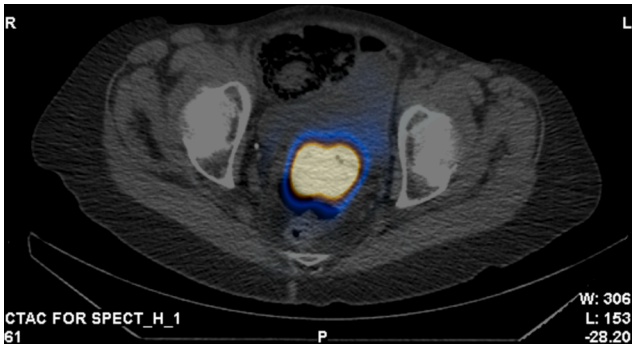

Fig. 1. Representative SPECT/CT Imaging. Technetium Tc 99m tilmanocept was found in high concentration in the cervix on preoperative imaging for all six patients.

Table 1 presents the demographic and baseline characteristics of the included patients. All patients had stage IA or IB endometrioid adenocarcinoma, FIGO grade 1 or 2. Two patients had lymphovascular invasion. Molecular characteristics were notable for two *POLE* mutant tumors, two tumors with mismatch repair deficiency, and two tumors with no specific molecular profile. All tumors demonstrated normal (wildtype pattern) p53 expression, and four tumors demonstrated aberrant (nuclear) beta catenin expression.

Table 2 lists the injection parameters of technetium Tc 99m tilmanocept, the overall detection of SLN by technetium Tc 99m tilmanocept and ICG, and location of identified SLN. Two patients underwent technetium Tc 99m tilmanocept injection the day before surgery and four patients on the day of surgery. There was no detection of technetium Tc 99m tilmanocept on SPECT/CT imaging or by intraoperative laparoscopic gamma counting in any of the included patients. SLNs were detected by ICG bilaterally in all six patients. The most common location of the detected SLNs by ICG was the external iliac region. The next most common location was obturator followed by common iliac areas. None of the six patients experienced adverse events or had symptoms of lymphedema or neuropathy at their postoperative follow up appointments.

To address why the technetium Tc 99m tilmanocept failed to be distributed into sentinel lymph nodes but was retained in high concentration in the cervical stroma, we performed additional mannose CD206 receptor immunohistochemistry staining. Using four-micron sections cut from FFPE blocks of cervical tissue, CD206 immunohistochemistry primarily highlighted tissue macrophages present throughout the full thickness of the cervical wall. No significant differences were noted between staining patterns in the endocervix, transformation zone, and ectocervix (Fig. 2A-C). The findings are similar to those in The Human Protein Atlas (The Human Protein Atlas - MRC1). While most endothelial cells were negative for CD206, rare endothelial cells and in some cases entire lymphatic vessel cross sections demonstrated positivity for CD206 (Fig. 2D), similar to that seen in the skin lymphatic channels on The Human Protein Atlas (The Human Protein Atlas - MRC1). Furthermore, there was no apparent difference in macrophage density in the cervical stroma and the subcutaneous tissue of the dermis which could explain the high retention of technetium Tc 99m tilmanocept in the cervical stroma as compared to its rapid clearance from the skin injection site in melanoma or breast cancer.

7. Discussion

In this trial, technetium Tc 99m tilmanocept did not result in SLN mapping in any of the first six patients, thereby resulting in an early discontinuation of this clinical trial for futility. Meanwhile, ICG injection resulted in bilateral SLN detection in all six cases. These results indicate that implementation of technetium Tc 99m tilmanocept into the SLN algorithm for endometrial cancer would not improve detection rates in endometrial cancer despite the agent's successful use for SLN detection in breast cancer, melanoma, and head and neck cancers.

While it is challenging to elicit the exact reason for the unsuccessful SLN detection by technetium Tc 99m tilmanocept, one possibility is sequestration by the specific binding to the mannose CD206 receptors on cervical macrophages and dendritic cells present throughout the cervical stroma. However, the density of cells carrying the mannose CD206 in the cervical stroma appeared similar to the density of cells carrying the mannose CD206 in the subcutaneous tissue, and other solid tumor types

Table 1
Demographics and Molecular Characteristics.

ID	Age	BMI	Race	CT A/P done?	Histology	Grade	TNM Stage	Myometrial Invasion	Lymphovascular Invasion	Cervical Involvement	Adnexal Involvement	Cytology Performed?	Molecular Characterization	Lymphedema or Neuropathy at Follow Up?	Adverse Events
1	51	21	White	No	Endometrioid	1	1A	Yes – 6 %	No	No	No	No	p53 wildtype pattern MLH1/MSH2/ MSH6/PMS2 intact *POLE* mutation positive (p,P286R) Beta catenin aberrant	No	No
2	68	50	Unknown	No	Endometrioid	2	1B	Yes – 50 %	Yes	No	No	No	p53 wildtype pattern MLH1/PMS2 absent MSH2/MSH6 intact *POLE* mutation negative Beta catenin aberrant	No	No
3	57	36	Unknown	No	Endometrioid	1	1A	No	No	No	No	No	p53 wildtype pattern MLH1/MSH2/ MSH6/PMS2 intact *POLE* mutation negative Beta catenin aberrant	No	No
4	56	24	Unknown	No	Endometrioid	1	1B	Yes – 77 %	No	No	No	No	p53 wildtype pattern MLH1/PMS2 intact MSH2/MSH6 absent *POLE* mutation negative Beta catenin wildtype	No	No
5	70	20	Unknown	No	Endometrioid	2	1B	Yes – 93 %	Yes	No	No	No	p53 wildtype pattern MLH1/MSH2/ MSH6/PMS2 intact *POLE* mutation positive (p.P286R) Beta catenin wildtype	No	No
6	49	32	Unknown	Yes	Endometrioid	2	1B	Yes – 61 %	No	No	No	No	p53 wildtype pattern MLH1/MSH2/ MSH6/PMS2 intact *POLE* mutation not assessed Beta catenin aberrant	No	No

Table 2
Injection Parameters and Sentinel Lymph Node Mapping.

ID	Technetium Tc 99m Tilmanocept Dose (mCi)	CTDI-vol (mGy)	DLP	SPECT/CT Mapping?	Overall Detection of Technetium Tc 99m tilmanocept?	Overall Detection of ICG?	Grossly Metastatic Disease Identified?	Right-sided SLN Locations (# of nodes)	Left-sided SLN Locations (# of nodes)	SLN Positive By
1	0.459	2.56	110.34	No	No	Yes	No	External Iliac (1)	Common Iliac (1)	ICG
2	0.523	6.36	273.88	No	No	Yes	No	External Iliac (2)	External Iliac (2), Hypogastric (1)	ICG
3	2.074	6.36	285.82	No	No	Yes	No	External Iliac (2)	Obturator (3), External Iliac (1)	ICG
4	0.428	2.71	114.56	No	No	Yes	No	Obturator (1), External Iliac (1)	Obturator (3), External Iliac (2)	ICG
5	2.086	2.02	85.35	No	No	Yes	No	Common Iliac (2)	External Iliac (2)	ICG
6	0.425	5.75	242.97	No	No	Yes	No	External Iliac (2)	External Iliac (2)	ICG

mCi = millicurie, CTDI-vol = Computed Tomography Dose Index-volume, mGy = milligray, DLP = dose length product, SPECT/CT = Single Photon Emission Computed Tomography/Computed Tomography.

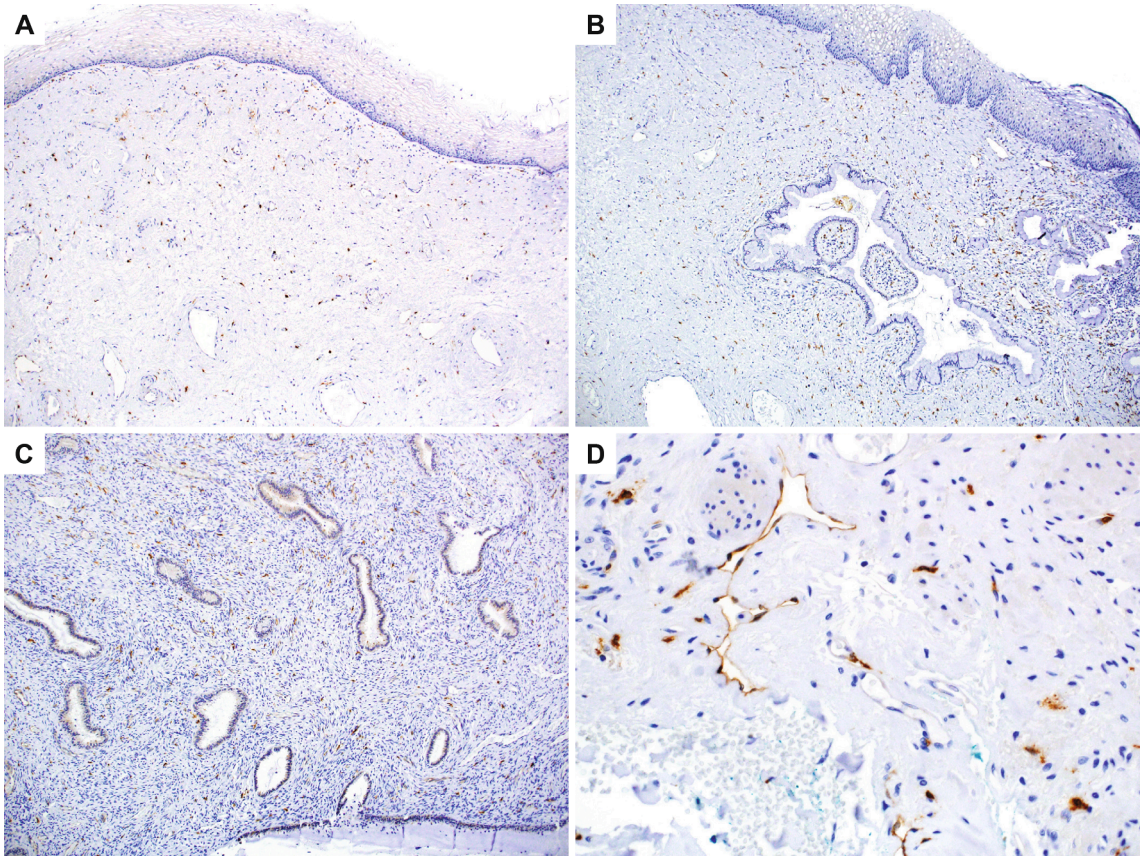

Fig. 2. Immunohistochemical staining for CD206 in cervical tissue from patients included in the study. CD206 stained primarily tissue macrophages, which were present throughout the full wall thickness of the cervix in the ectocervix (A), transformation zone (B), and endocervix (C). In some instances, focal staining of endothelial cells lining lymphatic channels was noted (D).

such as breast or melanoma which do not appear to trap technetium Tc 99m tilmanocept. The dextran backbone with 55 mannose molecules of the technetium Tc 99m tilmanocept may not be cleared as quickly from the injection site in the denser cervical stroma as compared to the loose subcutaneous tissue of the skin but trapped simply because of unfavorable hydrodynamics. Our trial is limited in its ability to address these possibilities, but future studies may consider utilizing additional radiolabeling techniques to further investigate the relationship between technetium Tc 99m tilmanocept and the mannose CD206 receptor protein in cervical tissue.

The lack of mapping with technetium Tc 99m tilmanocept was not dose-dependent, as patients who were injected with higher doses (4–5 times the mCi exposure) and underwent SPECT/CT the day before surgery also failed to map.

The unsuccessful mapping was also not due to inappropriate injection into the cervix as preoperative SPECT/CT imaging and intraoperative gamma probe surveys demonstrated high levels of radioactivity in the cervix (Fig. 1). The injection technique of

technetium Tc 99m tilmanocept was based on currently accepted techniques of cervical stromal injection. Interestingly, another trial has evaluated technetium Tc 99m tilmanocept in cervical cancer by injecting "peritumorally". This trial was terminated for unknown reasons. SLN detection with fluorescently labeled tilmanocept has been successfully noted in several animal models including rat and rabbit hind paws, canine prostates, and porcine bladders (Emerson, 2012; Liss, 2014; Liss, 2014; Lee, 2017). A single animal model study has demonstrated real-time intraoperative detection during robotic-assisted lymphadenectomy for endometrial cancer in a porcine model, thereby highlighting a possible mismatch between animal and human models (Anderson, 2018).

Notwithstanding technetium Tc 99m tilmanocept's efficacy, the successful bilateral SLN detection via ICG in all six of our patients supports the technique of single-agent mapping with intracervical ICG injections in early stage endometrial cancer patients. This is supported by the SHREC trial, in which the ICG bilateral mapping rate for SLN was 95 % with a sensitivity and negative predictive value of 100 % (Persson, 2019).

Limitations of this trial include the small sample size, which does not preclude possible future successful mapping with technetium Tc 99m tilmanocept. While the lack of SLN detection with technetium Tc 99m tilmanocept is not statistically significant based on prespecified analysis, it is a noteworthy diagnostic observation that may have clinical implications. This study's protocol was extrapolated from technetium Tc 99m tilmanocept injection protocols in other cancers, but evidence regarding whether this is truly applicable amongst patients with endometrial cancer is limited. The high rate of bilateral mapping with ICG alone would make it unlikely that dual mapping could significantly improve the detection rate. This limits the rationale for dual mapping with an additional agent associated with increased cost and patient burden. Despite this, it is important to note that when SLNs fail to map, current guidelines continue to recommend a complete lymphadenectomy on the side without detection, which means that the morbidity associated with this dissection remains unavoidable for many patients. One of our initial goals in undertaking this study was to see if we could improve the detection rate in such a way that meaningfully decreases the need for complete lymphadenectomy and thereby the complications that arise as a result of it. Our findings, however, instead contribute further to the growing body of literature that ICG remains a standard technique for SLN detection in early stage endometrial cancer.

CRediT authorship contribution statement

Ravali A. Reddy: Writing-original draft, Data curation, Formal analysis. **Stephanie Chow:** Investigation, Writing-review and editing. **Lucas Heilbroner:** Investigation. **Brooke Howitt:** Investigation, Writing-review and editing. **Elisabeth Diver:** Writing-review and editing. **Oliver Dorigo:** Writing-review and editing. **Babak Litkouhi:** Writing-review and editing. **Malte Renz:** Conceptualization, Methodology, Project administration, Writing-review and editing. **Amer Karam:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing-original draft, Writing-review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2022.101054.

References

Abu-Rustum, N.R., Khoury-Collado, F., Pandit-Taskar, N., Soslow, R.A., Dao, F., Sonoda, Y., Levine, D.A., Brown, C.L., Chi, D.S., Barakat, R.R., Gemignani, M.L., 2009. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol. Oncol. 113 (2), 163–169.

Albo, D., et al., 2001. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. Am. J. Surg. 182 (4), 393–398.

Anderson, K.M., et al., 2018. Molecular Imaging of endometrial sentinel lymph nodes utilizing fluorescent-labeled Tilmanocept during robotic-assisted surgery in a porcine model. PLoS ONE 13 (7), e0197842.

Baker, J.L., et al., 2015. Comparison of [(99m)Tc]tilmanocept and filtered [(99m)Tc] sulfur colloid for identification of SLNs in breast cancer patients. Ann. Surg. Oncol. 22 (1), 40–45.

Ballester, M., et al., 2011. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol. 12 (5), 469–476.

Barlin, J.N., et al., 2012. The importance of applying sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol. Oncol. 125 (30), 531–535.

Bats, A.S., et al., 2013. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. Ann. Surg. Oncol. 20 (2), 413–422.

Blessing, W.D., et al., 2002. A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. Am. J. Surg. 184 (4), 341–345.

Cabanas, R.M., 1977. An approach for the treatment of penile carcinoma. Cancer 39 (2), 456–466.

Chow, S., et al., 2022. Role of sentinel lymph node biopsy for gynecologic cancers. Curr. Opin. Obstet. Gynecol. 34 (1), 15–19.

Desai, P.H., et al., 2014. Accuracy of robotic sentinel lymph node detection (RSLND) for patients with endometrial cancer (EC). Gynecol. Oncol. 135 (2), 196–200.

Emerson, D.K., et al., 2012. A receptor-targeted fluorescent radiopharmaceutical for multi reported sentinel lymph node imaging. Radiology 265 (1), 186–193.

FDA, 2016. Prescribing information on Lymphoseek. 2016.

Holloway, R.W., et al., 2017. A Prospective Cohort Study Comparing Colorimetric and Fluorescent Imaging for Sentinel Lymph Node Mapping in Endometrial Cancer. Ann. Surg. Oncol. 24 (7), 1972–1979.

Holloway, R.W., et al., 2017. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol. Oncol. 146 (2), 405–415.

Hope-Ross, M., et al., 1994. Adverse reaction due to indocyanine green. Ophthalmology 101, 529–533.

International Atomic Energy Agency, 2015. Radiopharmaceuticals for sentinel lymph node detection: status and trends.

Jewell, E.L., et al., 2014. Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies. Gynecol. Oncol. 133 (2), 274–277.

Kitchener, H., et al., 2009. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373 (9658), 125–136.

Lee, H.J., et al., 2017. Fluorescence-based molecular imaging of porcine urinary bladder sentinel lymph nodes. J. Nucl. Med. 58 (4), 547–553.

Liss, M.A., et al., 2014. Preclinical evaluation of robotic-assisted sentinel lymph node fluorescence imaging. J. Nucl. Med. 55 (9), 1552–1556.

Liss, M.A., et al., 2014. Robotic-assisted fluorescence sentinel lymph node mapping using multimodal image guidance in an animal model. Urology 84(4): 982: e9-14.

Marcinow, A.M., et al., 2013. Use of a novel receptor-targeted (CD206) radiotracer, 99mTc-tilmanocept, and SPECT/CT for sentinel lymph node detection in oral cavity squamous cell carcinoma: initial institutional report in an ongoing phase 3 study. JAMA Otolaryngol Head Neck Surg 139 (9), 895–902.

Mikuta, J.J., 1993. International Federation of Gynecology and Obstetrics staging of endometrial cancer 1988. Cancer 71 (S4), 1460–1463.

Nagar, H., et al., 2021. *Sentinel node biopsy for diagnosis of lymph node involvement in endometrial cancer*. Cochrane Database Syst. Rev. 6, CD013021.

Panici, P.B., Basile, S., Maneschi, F., Lissoni, A.A., Signorelli, M., Scambia, G., Angioli, R., Tateo, S., Mangili, G., Katsaros, D., Garozzo, G., Campagnutta, E., Donadello, N., Greggi, S., Melpignano, M., Raspagliesi, F., Ragni, N., Cormio, G., Grassi, R., Franchi, M., Giannarelli, D., Fossati, R., Torri, V., Amoroso, M., Croce, C., Mangioni, C., 2008. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J. Natl Cancer Inst. 100 (23), 1707–1716.

Persson, J., et al., 2019. Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)-the final step towards a paradigm shift in surgical staging. Eur. J. Cancer 116, 77–85.

Plante, M., et al., 2015. Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature. Gynecol. Oncol. 137 (3), 443–447.

Renz, M., et al., 2019. Immediate intraoperative sentinel lymph node analysis by frozen section is predictive of lymph node metastasis in endometrial cancer. J Robot Surg.

Rossi, E.C., et al., 2017. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 18 (3), 384–392.

Siegel, R.L., Miller, K.D., Jemal, A., 2020. Cancer statistics, 2020. CA A Cancer J. Clin. 70 (1), 7–30.

Sinno, A.K., et al., 2014. A comparison of colorimetric versus fluorometric sentinel lymph node mapping during robotic surgery for endometrial cancer. Gynecol. Oncol. 134 (2), 281–286.
Tanner, E.J., et al., 2015. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. Gynecol. Oncol. 138 (3), 542–547.
The Human Protein Atlas - MRC1, Skin: https://www.proteinatlas.org/ENSG00000260314-MRC1/tissue/skin#img.
The Human Protein Atlas - MRC1, Cervix: https://www.proteinatlas.org/ENSG00000260314-MRC1/tissue/cervix.
Touhami, O., et al., 2015. Predictors of non-sentinel lymph node (non-SLN) metastasis in patients with sentinel lymph node (SLN) metastasis in endometrial cancer. Gynecol. Oncol. 138 (1), 41–45.
Vera, D.R., et al., 2001. A synthetic macromolecule for sentinel node detection: (99m)Tc-DTPA-mannosyl-dextran. J. Nucl. Med. 42 (6), 951–959.
Wallace, A.M., et al., 2003. Lymphoseek: a molecular radiopharmaceutical for sentinel node detection. Ann. Surg. Oncol. 10 (5), 531–538.
Wallace, A.M., et al., 2013. Comparative evaluation of [99m Tc] tilmanocept for sentinel lymph node mapping in breast cancer patients: results of two phase 3 trials. Ann Sure Oncol 20, 2590–2599.