Gynecol Surg (2016) 13:499–506
DOI 10.1007/s10397-016-0969-x

ORIGINAL ARTICLE

Sentinel lymph node biopsy in endometrial and cervical cancers using freehand SPECT—first experiences

Alexander Markus[1] · Alessandra Sophia Carmen Ray[1] · Daniele Bolla[1] · Joachim Müller[2] · Pierre-André Diener[3] · Thomas Wendler[4] · René Hornung[1]

Received: 3 May 2016 / Accepted: 19 July 2016 / Published online: 2 August 2016

Abstract The sentinel lymph node (SLN) biopsy (SLNB) is currently being developed for uterine cancers. The uterus is not easily accessible for tracer application; furthermore, the lymphatic drainage of the uterus is complex, which makes laparoscopic localization of the SLN challenging. The freehand single photon emission computed tomography (SPECT) is a 3D laparoscopic imaging modality which has been developed to overcome these problems. The aim of the study was to evaluate the freehand SPECT to detect the SLN in patients with uterine cancers. Twenty-nine patients with endometrial or cervical cancers were included into the LAPSENT study. Freehand SPECT was utilized to detect the SLN and guide its resection following intracervical injection of the tracer in patients with cervical cancer or hysteroscopy-guided injection of the tracer in patients with endometrial cancers. SLNs were detected in 18 of 24 patients with endometrial cancer and in 5 of 5 patients with cervical cancer. An average of 1.1 SLNs was detected in patients with endometrial cancers and 2 SLNs in patients with cervical cancers. The SLN was located in the pelvic lymphatic basin in 16 patients (12 unilateral and 4 bilateral). Three patients had paraaortic SLNs. Only one metastasis was found in any of the SLNs removed (endometrial cancer case) resulting in an upstaging. We demonstrated that SLNB in endometrial and cervical cancers using the freehand SPECT is feasible and that hysteroscopy-guided injection of the tracer is reasonable in endometrial cancers. Combining both techniques single-anesthesia SLNB of endometrial cancer is feasible.

Keywords Sentinel lymph node · Freehand SPECT · Endometrial cancer · Cervical cancer

✉ René Hornung
rene.hornung@kssg.ch

1 Department of Gynecology and Obstetrics, Cantonal Hospital, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland

2 Department of Radiology and Nuclear Medicine, Cantonal Hospital, St. Gallen, Switzerland

3 Department of Pathology, Cantonal Hospital, St. Gallen, Switzerland

4 Computer-Aided Medical Procedures (CAMP), Technical University of Munich, Munich, Germany

Introduction

Cervical cancer is the third most common cancer in women after breast and colorectal cancer worldwide, while endometrial cancer is the most common gynecologic cancer in developed countries. One of the most important prognostic factors for endometrial and cervical carcinoma is the presence of extrauterine disease, particularly pelvic or paraaortic lymph node metastases [1]. However, surgical lymph node assessment is controversial, particularly in women who are supposed to have an early stage disease [1]. Adverse effects of systematic radical lymphadenectomy such as lymphedema, extension of surgical time, risk of major vessel or nerve injury, and an overtreatment in node negative patients may be assessed more importantly than the survival benefit of the procedure. In order to overcome this controversy, the sentinel node biopsy (SLNB) has been proposed for these indications. The sentinel lymph node (SLN) concept is based on the hierarchic drainage of the lymphatic fluid from a defined anatomical basin. Hence, the first echelon lymph node, the so-called SLN, is most likely to contain potential metastases of the primary tumor. SLNB and the subsequent histopathological evaluation allow a prediction of the metastasis status of the remaining subordinate lymph nodes. SLNB has dramatically changed over the last 15 years, becoming a standard of care in several cancer types such as breast cancer or melanoma. SLNB avoids a radical lymphadenectomy, and hence, reduces morbidity, surgery time, and the rate of surgical complications. However, the SLNB procedure has not been established yet for pelvic malignances such as endometrial or cervical cancers (Table 1).

One of the main reasons for the slow introduction of SLNB for internal organs is the fact that opposite to tumors of the skin, internal organs such as the uterus are not easily accessible for tracer application. Furthermore, unlike the breast with its defined unilateral lymphatic drainage, the uterus is an unpaired midline organ with a much more complex lymphatic basin. The lymphatic basin encompasses the external and internal iliac vessels, the vena cava and the aorta up to the overcrossing of the left renal vein. In addition, the intraoperative laparoscopic localization of the SLN using only the audible signal of a gamma probe on the peritoneal surface is challenging due to the wide spreading lymphatic basin and the lack of depth information [2]. In order to overcome these problems, new innovative, 3D laparoscopic intraoperative imaging techniques have been developed. Freehand single photon emission computed tomography (SPECT) is a 3D intraoperative nuclear imaging modality based on a handheld gamma detector and surgical navigation technology [3]. After the injection of the radioactive tracer into the uterus, freehand SPECT detects the radioactivity emitted by the SLN and calculates in real time the exact position of the SLN in the patient. The position of the lymph node is demonstrated in a coordinate system overlaying the laparoscopic image on the surgical screen. Hence, the laparoscopic gamma detector can be easily guided to the sentinel lymph node based on this 3D navigation, enabling the accurate performance of the SLNB by laparoscopy. Moreover, the fact that freehand SPECT is an intraoperative imaging modality makes it possible to apply the radioactive tracer in the operating theater shortly before surgery optimizing logistics as a lymphoscintigraphy at the nuclear medicine department is not needed.

The aim of the LAPSENT study was to evaluate the feasibility of freehand SPECT to detect the SLN in patients with endometrial or cervical cancers and to evaluate the intraoperative application of the SLN tracer in endometrial cancers.

Material and methods

We designed a prospective single arm study ("LAPSENT" study) to investigate the feasibility of freehand SPECT-guided SLNB in patients with endometrial or cervical cancers. The study was performed in the department of Obstetrics and Gynecology, Cantonal Hospital of St. Gallen, Switzerland. The female patients were assigned into two groups: Group 1 included patients with endometrial cancers for whom, following our guidelines, a systematic pelvic and paraaortic lymphadenectomy was not necessary. Group 2 included patients with endometrial cancers who qualified for systematic pelvic and paraaortic lymphadenectomy or patients with cervical cancers who underwent systematic pelvic lymphadenectomy. Inclusion criteria were: patients over the age of 18 years, without history of hysterectomy or retroperitoneal lymphadenectomy, with a histologically confirmed endometrial or cervical cancer, preoperative decision of our tumor conference, good compliance, with a signed written informed consent, and without mental incapacity. Exclusion criteria were: Inoperability, rejection by the patient to participate in the study, a documented hypersensitivity to the radioactive tracer (here Technetium-99m Nanocoll®, GE Healthcare, Hamburg, Germany), pregnancy, or breastfeeding. The study has been approved by the local ethics committee.

The freehand SPECT system (declipse®SPECT Laparoscopy, SurgicEye GmbH, Munich, Germany) is depicted in Figs. 1 and 2 and is described in detail elsewhere [3–6]. The system consists of an optical tracking system including the data-processing unit (part A in Fig. 1), attached to an optical camera (part B in Fig. 1) that is placed above the patient (similar to an operating light, see part D Fig. 2), and a handheld gamma detector (here a laparoscopic gamma probe) with an optical reference (part C in Fig. 1, part B in Fig. 2). The gamma probe is connected to a standard gamma counter used for sentinel lymph node biopsy (part D in Fig. 1). An optical patient reference (part E in Fig. 1) is taped on the patient's skin of the left lower abdomen (optional). The optical tracking system determines the position and orientation of the gamma probe with the help of infrared light. The infrared light emitted by two light sources adjacent to the optical camera (part B in Fig. 1) is reflected by three biocompatible and passive sphere markers that are mounted on the gamma probe reference as well as on the patient reference. The three reflective spheres allow an accurate 3D orientation of the gamma probe as well as of the patient. The light reflected from the spheres is detected by the optical camera and is converted to an electrical signal that is processed in the data-processing unit. The data processor generates an image from the raw data. From the two infrared-based images, the system is capable to calculate the 3D position and orientation of both, the probe and patient.

The handheld gamma probe (laparoscopic probe with 45° angled collimator at the tip of the probe, Crystal Photonics GmbH, Berlin, Germany; part C in Fig. 1, part F in Fig. 2) serves as a detector for ionizing radiation (expressed as counts per second) and is connected to a standard system for SLNB (Crystal probe automatic SG04, Crystal Photonics GmbH, Berlin, Germany). The user scans the lymphatic basin of the pelvis and the paraaortic region using the gamma probe during laparoscopy. The anatomic site is scanned in at least two different angles of projection by turning the probe along its axis to acquire sufficient 3D information for later image reconstruction. The data-processing unit acquires data of both, the gamma probe and the optical tracking

Table 1 Table summarizes advantages and disadvantages of various techniques for SLN detection in patients with endometrial cancers

Route of tracer application/technique of SLN detection	Advantage	Disadvantage	References (exemplary)
Route of tracer application			
Ultrasound-guided intramyometrial injection	No anesthesia required Application the day prior to surgery with preoperative SPECT-CT	Painful procedure Technically challenging	[10]
Open or laparoscopic subserosal injection	Technically easy Under general anesthesia Tracer application and main surgery during one single procedure	Extends anesthesia and surgery time No preoperative SPECT available Unknown lymphatic drainage (serosa vs. endometrium) Low SLN detection rate	[11]
Intracervical	Easily applicable SPECT possible the before surgery No anesthesia required	Paraaortic SLN detection rate in endometrial cancers less frequent	[13–15]
Subendometrial injection	Mimics "natural" lymphatic drainage of endometrial cancer	Requires hysteroscopy Requires general anesthesia Preoperative SPECT not possible	[17, 18]
Technique of SLN detection			
Isosulfan blue	Various ways of application of tracer possible Stains lymph nodes and lymphatic vessels facilitating SLN detection	Wide opening Of retroperitoneal space required SLN detection may be cumbersome in obese patients A lot of tissue stains blue	[12, 19, 20]
Indocyanine green	Tissue stains only in fluorescence detection mode Easy detection of SLN Various ways of application of tracer possible	Requires special equipment and light switch Wide opening of retroperitoneal space needed SLN detection may be cumbersome in obese patients	[18, 19, 21–23]
Radioactive tracer with regular gamma probe for SLN detection	allows quick scanning of lymphatic basin Various ways of application of tracer possible Very small retroperitoneal opening needed Detection in obese patients possible	shadowing of SLN by radiation of injection site Requires radiopharmacon and cooperation with department of nuclear medicine with according safety regulations No SPECT	[3, 24, 25]
Freehand SPECT	Provides real-time 3D detection of SLN Assists SLN localization Application of tracer and SPECT and surgery in a single procedure Very small incision of the peritoneum needed	Special instrumentation required Requires radiopharmacon and cooperation with department of nuclear medicine with according safety regulations	LAPSENT study

Fig. 1 The used freehand SPECT system used for laparoscopic sentinel lymph node detection. The system consists of an optical tracking system including the data-processing unit (part *A*), attached to an optical camera (part *B*) that is placed above the patient (similar to an operating light), and a hand-held gamma probe (part *C*) with little spheres serving as an optical reference (part *C*). The gamma probe is connected to a standard gamma detector (part *D*) used for sentinel lymph node biopsy. An optical patient reference (little spheres shown in part *E*) is taped on the patient's skin of the left lower abdomen. The optical tracking system determines the position and orientation of the gamma probe with the help of infrared light. The infrared light emitted by two light sources adjacent to the optical camera (part *B*) is reflected by three sphere markers, detected by the optical camera, and converted to an electrical signal that is processed in the data-processing unit

system. From these datasets, the system enables the generation of 3D images showing the radioactivity distribution inside the patient in real time.

Patients with cervical cancers received an injection into the four quadrants of the uterine cervix with a cumulative dose of 80 MBq of Technetium-99m Nanocoll® (tracer) the day

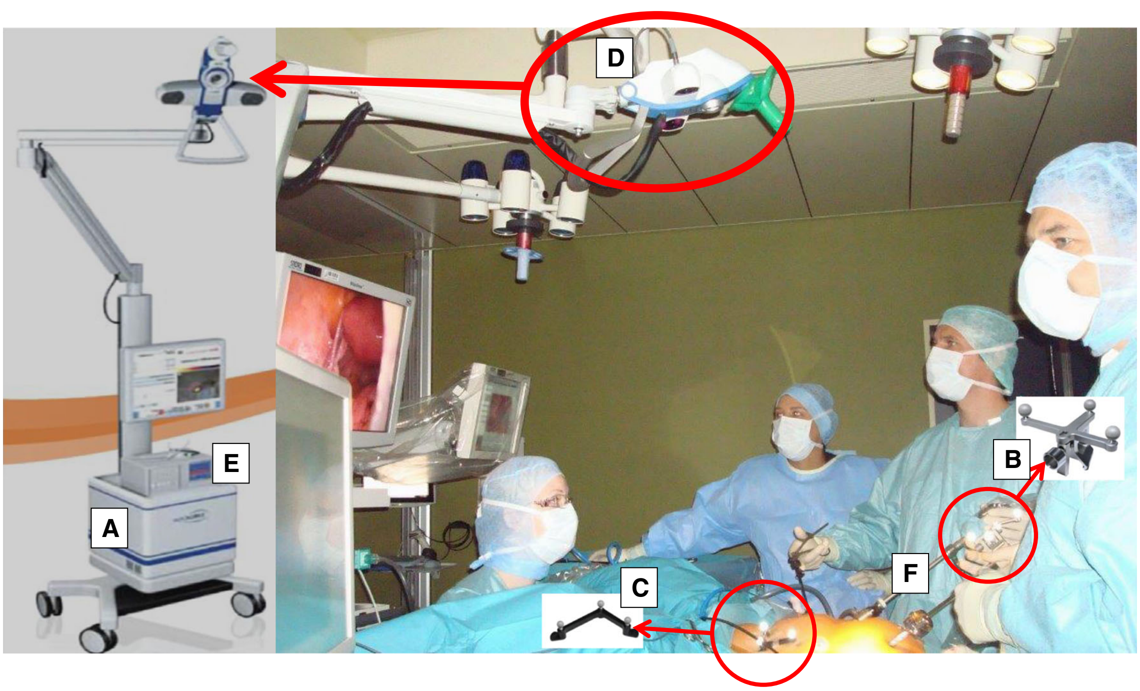

Fig. 2 The freehand SPECT system as it is used in the operation theater. Part *A* is the data-processing unit, part *B* corresponds to the optical reference spheres mounted on the gamma probe, part *C* is the optical reference taped on the patient's skin, part *D* is the optical camera placed above the patient, part *E* corresponds to the gamma detector, and part *F* is the endoscopic camera used for laparoscopy

before surgery. This procedure has been performed in an outpatient setting in the Department of Nuclear Medicine. During a routine gynecologic examination performed by an experienced gynecologist, the uterine cervix has been exposed using a regular speculum and has been injected painless without any anesthesia. Following removal of all instruments, dynamic scintigrams of the patient were recorded immediately after the injection, 20 pictures every 30 s and subsequently until SLN(s) were detected. Then a low-dose SPECT-CT was acquired allowing a correlation of the sentinel lymph node localization detected by conventional SPECT with the localization of the SLN(s) detected by the freehand SPECT 3D laparoscopic intraoperative imaging system.

Patients with endometrial cancers received a hysteroscopically guided injection (36 cm long Charriere 3 needle) of the tracer adjacent to the tumor into the subendometrial layer in cases where the tumor was confined to a small area of the uterine cavity. In case of large cancers that encompass major parts of the uterine cavity, 40 MBq of the radioactive tracer was injected into the anterior as well as into the posterior wall of the uterus with a cumulative dose of 80 MBq of Technetium-99 m Nanocoll® (tracer) at the beginning of the surgery. Figure 3 panel A–C shows a hysteroscopy with various aspects of an endometrial cancer, and in panel D, the needle ready to inject the tracer adjacent to the tumor. The procedure was performed in the operation room while the patient was under general anesthesia for the main surgical procedure. The injection of the tracer in the operation room was performed under the close supervision of a nuclear medicine physician. Thirty minutes after the hysteroscopical injection of the tracer (this is the approximate time usually required to prepare the patient for a standard laparoscopic surgery), the SLN was localized through the 3D freehand SPECT laparoscopic intraoperative imaging system. Thereafter, the patient underwent standard surgical procedure according to her disease.

The SLN detection was performed in both patients, those with cervical and those with endometrial cancer in the same way. The lymphatic basin was scanned using the laparoscopic gamma probe. The right pelvic wall was scanned, followed by the left pelvic wall as well as the paraaortic region, respectively. Each area was scanned in two different orientations of the probe to collect 3D information in the x, y, and z axis of the probe. A total of at least 3,000 counts were collected per area (~150 s). On the screen of the system, the hot spot is displayed as a green spot with a number expressing the emitted radiation of the hot spot in relation to the background radiation (emitted by the surrounding tissue) and the radiation emitted by the other spots, as well as the distance between the gamma probe and the detected hot spots. In addition, the gamma probe emits an audible signal that helps confirm the freehand SPECT finding. Once detected, the SLN was selectively excised, removed from the abdominal cavity, and prepared for pathologic examination. Pathologic processing of the SLN has been performed following the guidelines of the Swiss Pathology Society with serial sectioning of the SLN in 200 μm intervals. The tissue was stained with routine H&E, as well as with immunohistochemistry for pancytokeratin (MNF116).

All patients underwent standard surgical procedures. Patients with cervical cancer had a full pelvic lymphadenectomy followed by a radical hysterectomy Piver III (Wertheim–Meigs–Okabayashi). Patients with type I endometrial cancers underwent a hysterectomy with bilateral salpingo-oophorectomy and an intraoperative frozen section. Type I endometrial cancers with grading 2 or 3, and/or infiltration of more than half of the myometrium, as well as all type II cancers underwent a full pelvic and paraaortic lymphadenectomy up to the left renal vein. A postoperative tumor board was held to decide whether or not an adjuvant treatment was necessary following international guidelines. Data was compiled in

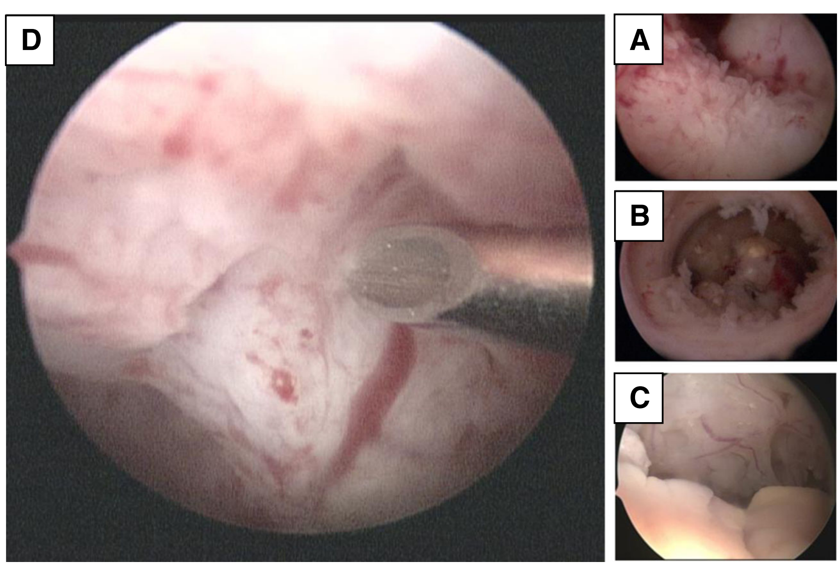

Fig. 3 Fig. 3 shows hysteroscopic site of three endometrial cancers (panels *A*–*C*) and the needle ready to inject the radioactive tracer adjacent to the tumor into the submucosal layer of the uterine cavity (panel *D*)

an Excel sheet and routine statistical analysis was performed.

Results

A total of 29 patients was included to date in the LAPSENT study, 24 patients with endometrial cancer (group 1) and 5 with a cervical carcinoma (group 2). The mean age was 56 years. Twenty-two of the 24 patients with endometrial cancers were operated by laparoscopy, while 2 were operated by open surgery. All 5 patients with cervical cancer underwent laparoscopic surgery. There was no incidence of intraoperative complications in either group. We could detect in average 1.1 SLNs in patients of group 1 and 2 SLNs in patients of group 2. The SLNB procedure was carried out in all patients. However, SLNs were detected in 18 of 24 patients in group 1 and in all patients of group 2, resulting in a detection rate of 79 %. Radical lymphadenectomy was performed in 5 patients of group 1 and in all patients of group 2. The average number of SLNs removed was 2.1 with a standard deviation of 1.3. The SLN was located in the pelvic lymphatic basin in 16 patients of which 12 SLNs were unilateral and 4 were located on both pelvic walls, i.e., bilaterally. No additional SLNs were found ex vivo in the resected tissue for the patients that underwent radical lymphadenectomy. Three patients of group 1 had paraaortic SLNs. Only one metastasis was found in any of the SLNs removed.

Discussion

According to guidelines, endometrial cancers of the uterus are usually staged and treated by hysterectomy, bilateral salpingo-oophorectomy with or without pelvic, and paraaortic lymphadenectomy. Lymph node assessment is important to determine the patient's prognosis, to tailor adjuvant therapies, and to remove metastasis. However, the therapeutic value of systematic lymphadenectomy, particularly in women presumed to have low risk and early stage disease, is controversial [1, 7, 8]. Lymphadenectomy, however, is a surgical procedure with substantial adverse effects. Lymphadenectomy significantly increases the risk for lower limb lymphedema and lymphoceles. In addition, transperitoneal lymphadenectomy substantially increases the time of surgery and anesthesia, has a complication rate of about 9 %, and therefore, generates costs. A model to predict the individualized risk of lymph node metastasis has been proposed by a group from the Mayo Clinic [9]. This model stratifies each patient into a risk group, which however, still does not definitively diagnose the lymph node status of the patient. Thus, the lymph node status has to be evaluated by histology. Another approach to benefit from the nodal status and to avoid unnecessary surgery is the SLN concept. The SLN procedure has dramatically changed over the last 15 years. Today, SLN biopsy has become the golden standard for many cancers such as breast cancer, melanoma, head and neck tumors and others.

The sentinel concept for tumors of internal organs is somewhat different to that of rather superficially localized tumors such as cancers of the breast or skin. Superficial tumors are easily accessible for the application of the tracer by a simple subcutaneous injection adjacent to the tumor site. The application of the tracer into the uterine cavity, on the other hand, requires analgesia, special equipment, and well-trained personal and special skills. The lymphatic basin of superficial tumors is well known, defined to a small area of one side of the body, and relatively easily accessible for surgery. The uterus is an internal midline organ with a complex lymphatic drainage system that is only accessible for well-trained surgeons, especially, when performed by a minimal-invasive procedure. Lymph node metastasis may occur along the uterine artery and vein, the internal, as well as the external iliac vessels, and the common iliac vessels. Lymph node metastasis may occur on either one of the patient's side, or on both sides, and may continuously be found along the aorta and/or the cava vein. In addition, cancers of the uterine cavity may, unlike cervical cancers but similar to ovarian cancers, metastasize directly along the ovarian vessels to the paraaortic region adjacent to the renal vein. Thus, the area, where the SLN may be found is extensive. While the sentinel concept is well defined for many tumors, there are many variables that are not yet standardized for uterine cancers (e.g., amount of tracer to be injected, best injection site, interval between tracer injection, and earliest time point when sentinels may be found and so on).

Ultrasound-guided tracer application has been suggested by Torné et al. [10]. Tracer application was successful in 90 % of the cases, allowing a preoperative lymphoscintigraphy, followed by laparoscopic pelvic and paraaortic lymphadenectomy the day after injection. The ultrasound-guided injection of the tracer, however, caused significant pain (visual analog scale 4.3, range 1–10), and thus, seemed not to be applicable for routine clinical use. Subserosal injection of the radiotracer during laparotomy has been proposed by Burke et al. [11]. But due to a low SLN detection rate, this technique has been abandoned [12]. Preoperative intracervical injection of the radiotracer is another application mode that has been suggested by several groups [13–15]. This easy way of the tracer application raises a major concern whether or not the pattern of lymphatic drainage is representative for cancers of the uterine cavity if the tracer has been applied to the uterine cervix. Especially, direct drainage of lymph to the paraaortic region while sparing the pelvic lymphatic basin occurs in some cases of endometrial cancers, but is infrequently found when the tracer is injected into the uterine cervix rather than into the endometrial or myometrial tissue [16, 17]. Injection of the radiotracer underneath the endometrium or into the myometrium can be performed under visual control during hysteroscopy. This mimics the natural lymphatic drainage with a relevant number of paraaortic lymph nodes [17, 18]. This application mode, however, is a procedure requiring anesthesia. Because of this, the entire surgical procedure (application of the tracer in a first step, lymphoscintigraphy the day after tracer application, and the main laparoscopic surgery with sentinel detection and hystero-salpingo-oophorectomy as a second step) requires two separate anesthesia. For our study, we chose a different setup. We injected the radiotracer at the beginning of the main surgery by hysteroscopy and continued directly to the laparoscopic main procedure. Because we utilized the freehand SPECT, we were able to omit the lymphoscintigraphy and to perform the entire procedure under a single anesthesia. We consider this as the main advantage of our study setup and a real progress in the development of the sentinel concept for pelvic tumors.

Many groups are currently working to develop the sentinel concept for uterine tumors. Various tracing agents have been proposed. Isosulfan blue dye can be applied without special precautions and stains the sentinel lymph node as well as the lymphatic vessels draining the tumor site towards the sentinel lymph node which is helpful to find it [12, 19, 20]. Indocyanine green is a fluorescent agent that can also be used to stain sentinel lymph nodes. However, to detect the fluorescent dye, the laparoscope has to be equipped with a near-infrared fluorescence imaging system [18, 19, 21–23]. Both dyes, the isosulfan blue and the indocyanine green, have the main disadvantages that searching for the SLN in a wide area is cumbersome, that the entire lymphatic basin has to be exposed by opening the peritoneum over the vessels, and that the system lacks of depth information which makes it even more difficult in obese patients. Radioactive tracers, on the other hand, allow a quick scanning of the lymphatic basin with the gamma-probe to localize the hot spots where the SLN is localized while the peritoneum has not to be opened. Unlike the above-mentioned dyes, radioactivity allows the detection of SLNs also in the depth of the tissue even in obese patients as the penetration of light in tissue is only few millimeters—a thin layer of tissue is sufficient to “hide” a stained SLN. However, the effects of “shine-trough” (whereby the high radioactive levels from the injection site or other sources are detected from below the tissue of interest) and “shadowing” (SLNs masked by a nearby injection site) made it challenging to detect the SLN [3, 24, 25]. In order to overcome these problems, an innovative 3D intraoperative nuclear imaging model based on a handheld gamma detector and surgical navigation technology has been developed [3]. Freehand SPECT provides a 3D image to ease and quicken the localization of the SLN in real time. In addition, the surgeon is guided towards the SLN by the system. The inclusion of imaging in the operating room favors the sensitivity of intraoperative detection of SLN(s), even if it is located close to the injection site. In addition the image-guidance and the availability of depth information enable a fast and intuitive roll-up of this procedure. It has been successfully used for the intraoperative detection of SLNs in patients with breast cancer and melanoma in open surgery. To the best of our knowledge, we are the first clinic that uses freehand SPECT laparoscopically in patients with endometrial or cervical cancers.

Our SLN detection rate of 79 % and the distribution to one or both pelvic sides is within the range of that published by other groups [22, 26]. In our study, 3 out of 24 patients with endometrial cancers had paraaortic SLNs which seems to be a higher rate than that reported by other groups [22]. Although limited by the small number of patients included in our study, we believe that this rather high number of paraaortic SLNs in our study is due to the subendometrial injection of the tracer, and thus, represents the true lymphatic drainage of endometrial malignancies.

We found one case that would normally not undergo systematic lymphadenectomy with a metastasis in the SLN. Leading to a more accurate staging this patient was upstaged and profited from our study. Encouraged by this case, as well as by our detection rates and a technology that facilitates laparoscopic SLN detection in patients with either cervical or endometrial cancers, we continue to enroll patients into the LAPSENT study while considering improvements of the process.

In our study, we demonstrated that SLNB in endometrial and cervical cancers using freehand SPECT is feasible and that hysteroscopy-guided injection of the tracer is reasonable in endometrial cancers. Further optimizations of variables in the process and inclusion of more patients are under way.

Compliance with ethical standards

Funding This study has no special funding.

Conflict of interest Thomas Wendler has a minor share (<5 %) of SurgicEye GmbH. The other authors declare that there are no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373(9658):125–136
2. Levenback CF (2008) Status of sentinel lymph node biopsy in gynecological cancers. Ann Surg Oncol 15(1):18–20
3. Wendler T, Herrmann K, Schnelzer A, et al. (2010) First demonstration of 3-D lymphatic mapping in breast cancer using freehand SPECT. Eur J Nucl Med Mol Imaging 37(8):1452–1461
4. Freesmeyer M, Winkens T, Opfermann T, Elsner P, Runnebaum I, Darr A (2014) Real-time ultrasound and freehand-SPECT. Experiences with sentinel lymph node mapping. Nuklearmedizin Nucl Med 53(6):259–264
5. Gillard C, Franken P, Darcourt J, Barranger E (2015) Freehand SPECT for navigation and sentinel node detection in breast cancer. Gynecol Obstet Fertil 43(2):172–175
6. Pouw B, der Veen LJ, Hellingman D, et al. (2014) Feasibility of preoperative (125)I seed-guided tumoural tracer injection using freehand SPECT for sentinel lymph node mapping in non-palpable breast cancer. EJNMMI Res 4:19
7. Benedetti Panici P, Basile S, Maneschi F, et al. (2008) Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst 100(23):1707–1716
8. Todo Y, Kato H, Kaneuchi M, Watari H, Takeda M, Sakuragi N (2010) Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet 375(9721):1165–1172
9. AlHilli MM, Podratz KC, Dowdy SC, et al. (2013) Risk-scoring system for the individualized prediction of lymphatic dissemination in patients with endometrioid endometrial cancer. Gynecol Oncol 131(1):103–108
10. Torne A, Pahisa J, Vidal-Sicart S, et al. (2013) Transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR): a new method for sentinel lymph node detection in endometrial cancer. Gynecol Oncol 128(1):88–94
11. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gershenson DM (1996) Intraabdominal lymphatic mapping to direct selective pelvic and paraaortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. Gynecol Oncol 62(2):169–173
12. Frumovitz M, Bodurka DC, Broaddus RR, et al. (2007) Lymphatic mapping and sentinel node biopsy in women with high-risk endometrial cancer. Gynecol Oncol 104(1):100–103
13. Kadkhodayan S, Shiravani Z, Hasanzadeh M, et al. (2014) Lymphatic mapping and sentinel node biopsy in endometrial cancer—a feasibility study using cervical injection of radiotracer and blue dye. *Nuclear medicine review*. Cent East Eur 17(2):55–58
14. Lopez-Dela Manzanara Cano C, Cordero Garcia JM, Martin-Francisco C, Pascual-Ramirez J, Parra CP, Cespedes CC (2014) Sentinel lymph node detection using 99mTc combined with methylene blue cervical injection for endometrial cancer surgical management: a prospective study. Int J Gynecol Cancer: Off J Int Gynecol Cancer Soc 24(6):1048–1053
15. Mucke J, Klapdor R, Schneider M, et al. (2014) Isthmocervical labelling and SPECT/CT for optimized sentinel detection in endometrial cancer: technique, experience and results. Gynecol Oncol 134(2):287–292
16. Bats AS, Clement D, Larousserie F, et al. (2008) Does sentinel node biopsy improve the management of endometrial cancer? Data from 43 patients. J Surg Oncol 97(2):141–145
17. Niikura H, Kaiho-Sakuma M, Tokunaga H, et al. (2013) Tracer injection sites and combinations for sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol 131(2):299–303
18. Rossi EC, Jackson A, Ivanova A, Boggess JF (2013) Detection of sentinel nodes for endometrial cancer with robotic assisted fluorescence imaging: cervical versus hysteroscopic injection. Int J Gynecol Cancer: Off J Int Gynecol Cancer Soc 23(9):1704–1711
19. Holloway RW, Bravo RA, Rakowski JA, et al. (2012) Detection of sentinel lymph nodes in patients with endometrial cancer undergoing robotic-assisted staging: a comparison of colorimetric and fluorescence imaging. Gynecol Oncol 126(1):25–29
20. Sinno AK, Fader AN, Roche KL, Giuntoli RL 2nd, Tanner EJ (2014) A comparison of colorimetric versus fluorometric sentinel lymph node mapping during robotic surgery for endometrial cancer. Gynecol Oncol 134(2):281–286
21. Papadia A, Imboden S, Siegenthaler F, et al (2016) Laparoscopic indocyanine green sentinel lymph node mapping in endometrial cancer. Ann Surg Oncol 23(7):2206–2211
22. Plante M, Touhami O, Trinh XB, 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
23. Rossi EC, Ivanova A, Boggess JF (2012) Robotically assisted fluorescence-guided lymph node mapping with ICG for gynecologic malignancies: a feasibility study. Gynecol Oncol 124(1):78–82
24. Alkureishi LW, Burak Z, Alvarez JA, et al. (2009) Joint practice guidelines for radionuclide lymphoscintigraphy for sentinel node localization in oral/oropharyngeal squamous cell carcinoma. Ann Surg Oncol 16(11):3190–3210
25. Balch CM, Morton DL, Gershenwald JE, et al. (2009) Sentinel node biopsy and standard of care for melanoma. J Am Acad Dermatol 60(5):872–875
26. Ansari M, Rad MA, Hassanzadeh M, et al. (2013) Sentinel node biopsy in endometrial cancer: systematic review and meta-analysis of the literature. Eur J Gynaecol Oncol 34(5):387–401