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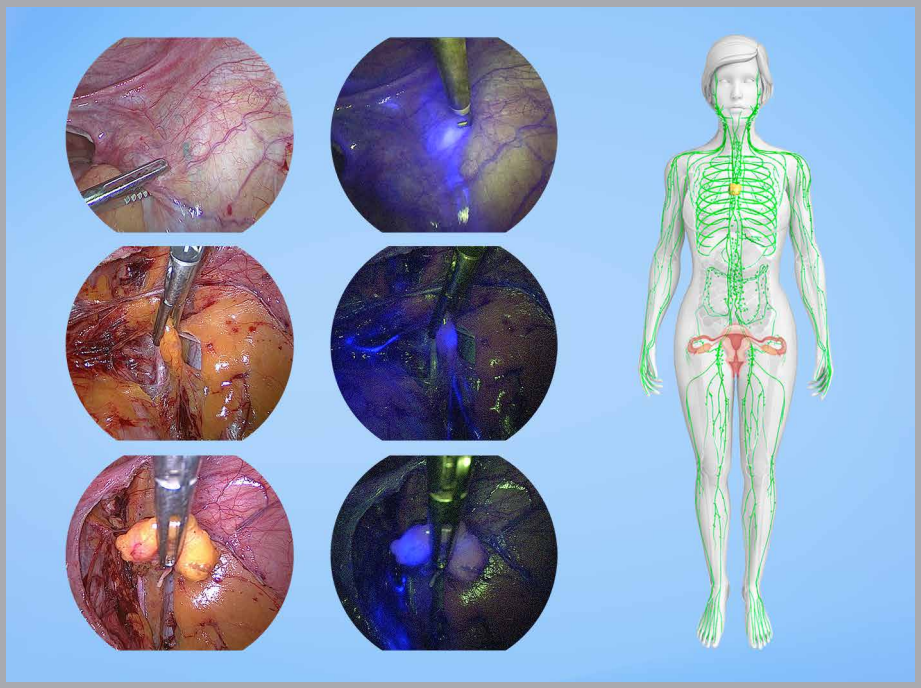
ICG-ENHANCED FLUORESCENCE-GUIDED SLN MAPPING IN GYNECOLOGICAL MALIGNANCIES

2nd Edition



Andrea PAPADIA
Michael D. MUELLER

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Second Edition

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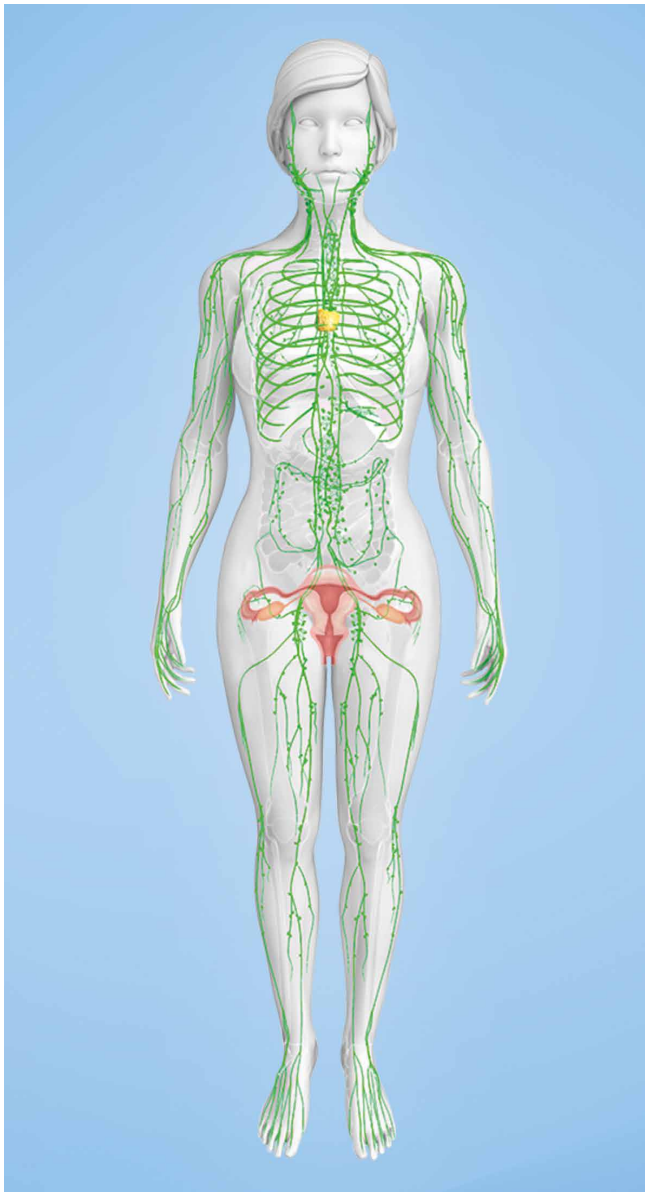
Preface

As with the majority of solid tumors, surgical lymph node assessment is of utmost importance in patients treated for cervical and / or endometrial cancer. In both pathological entities, lymph node status constitutes one of the most important prognostic factors. However, in most cases, the lymph nodes are negative for tumor involvement. In these patients, routine systematic lymphadenectomy has been shown to result in a prolonged duration of surgery, additional costs and an increase in the rate of intraoperative and long-term postoperative complications, such as bleeding, ureteral and nerve injury, lower-extremity lymphedema, lymphocele formation and sensory loss.

In recent decades, growing efforts have been geared towards improving long-term prognosis and quality of life for gynecologic oncology patients. An excellent example of this less-invasive and tissue-sparing approach is the significant change that was seen in the surgical treatment of patients with breast cancer. Since the pioneering days of breast surgery, when every breast cancer patient was subjected to a radical mastectomy (Rotter-Halsted operation) – which included the excision of the entire breast along with the pectoralis major and minor muscles, as well as a concomitant radical axillary lymphadenectomy – we have gone through transitory phases until arriving at the current surgical approach: the lumpectomy with a sentinel lymph node (SLN) biopsy. This body shape-sparing approach not only leads to a more favorable cosmetic result, but also allows to yield an improved functional outcome. Since lymph node assessment is performed via SLN mapping, the incidence rate of upper extremity lymphedema is of insignificant value.

In the armamentarium of therapeutic modalities available for cancer patients, less turned out to be more. Smaller incisions and a reduced number of lymph nodes removed have lead to improved surgical results with reduced blood loss, shortened hospital stays and faster recovery. While offering the same oncological outcomes as with open surgery procedures, a minimally invasive approach, by means of ultra-staging, allows to yield more accurate information on the pathology to be treated, and facilitates identification of aberrant lymphatic vessels that originate from SLN located at an abnormal site. On account of these benefits, SLN mapping in conjunction with a minimally invasive approach has been found to lead to improved functional outcomes through a reduced rate of lower-extremity lymphedema and, in view of smaller incisions, to a better overall cosmetic result.

The Authors



Schematic representation of the female lymphatic system.

1 Introduction

Over the past decades, minimally invasive surgery has gained widespread acceptance in the field of gynecology. After an initial period of reluctance, the technique established itself as a valid method that is used in gynecologic oncology as well. It has been shown that oncologic procedures such as pelvic / para-aortic lymph node dissection can be performed safely and effectively using a minimally invasive technique.[47] Hence, the technique has become the first-line standard of care in the treatment of specific pathologies such as endometrial cancer.[61,62] The outcomes of minimally invasive procedures have solidly demonstrated that the technique is linked with reduced blood loss, shorter hospital stay, faster recovery and improved cosmetic results while offering an equivalent oncological outcome.[47]

Recent publications in the scientific literature suggest that sentinel lymph node (SLN) mapping has gained in significance and is being increasingly used in clinical gynecologic oncology.[29,49] By identifying the first lymph node draining the tumor, lymphatic mapping with SLN biopsy allows to reduce the morbidity associated with a complete lymphadenectomy and to improve detection of metastatic disease (through ultrastaging protocols and identification of alternate sites of lymphatic drainage). Lymphatic mapping and SLN biopsy were first reported by *Cabanas* in 1977 for penile carcinoma[10] and has since then become the first-line treatment option in the presence of various malignancies.[28] Vast evidence suggests that SLN biopsy can be safely integrated in the management strategy for endometrial cancer and/or early stage cervical cancer.[12–15,28,29]

Historically, SLN mapping was performed with ^{99m}Technetium radiocolloid (^{99m}Tc) alone or in combination with blue dyes. However, the use of these tracers is associated with a few side effects. Blue dyes cause discoloration of skin and urine, a decrease in pulse oximetry readings and, occasionally, trigger severe allergic reactions.[2,11,40] Lymphatic mapping with ^{99m}Tc is logistically complicated because strict adherence to a specialized coordination protocol in a controlled environment is required during injection, video image acquisition and surgery, making the technique time-consuming and expensive. ICG is currently used in various oncologic specialties as an imaging agent for intraoperative lymphatic mapping. It is bound almost completely to large plasma proteins causing the agent to be confined within the intravascular space. For more than 20 years, ICG is employed as a tracer in ophthalmology for retinal and choroidal angiography.

1.1 The Fluorescence Phenomenon

In 1852, *George Gabriel Stokes* described the mineral Fluorite as emitting blue light following exposure to ultraviolet light.[56,57] He called the phenomenon "Fluorescence" and coined the term "Fluorophores" for substances exhibiting this feature.

The property to emit fluorescence is very common in nature. The sensitivity of delocalized electrons in aromatic ring structures is responsible for this. Once light energy is absorbed by the fluorochrome's organic molecules, a promotion of delocalized electrons from ground state to a higher energy level occurs. Upon return from excited singlet state to ground state, energy is emitted in the form of photons reaching the observer's eye as fluorescence. The emitted fluorescence is lower in energy because a part of the absorbed exciting light energy is converted to heat.

Aromatic ring structures are key components of biological substances such as DNA, proteins and sugars. Since the 1960s, the property of these substances to emit fluorescent light has been used for real-time fluorescence imaging in life sciences and medicine. The oldest known FDA-approved near-infrared (NIR) fluorescent dye used in medicine is indocyanine green (ICG).

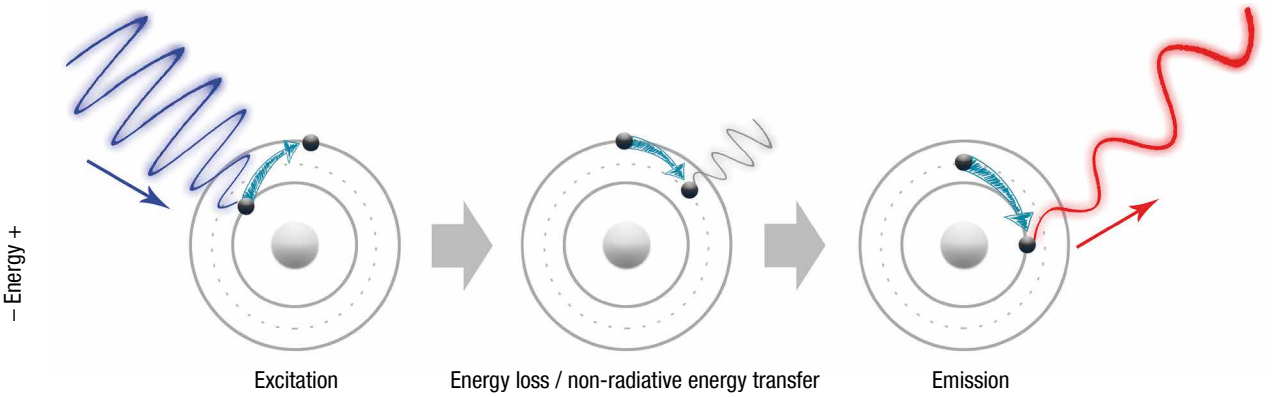


Fig. 1.1 Schematic drawing demonstrating the principle of fluorescence.

1.2 Indocyanine Green and Near-Infrared Fluorescence

Indocyanine green is a fluorescent marker that has been used for decades in medicine. It was first approved by the FDA for angiographies in 1959 and is nowadays used for various types of applications. It is widely adopted for angiographies in ophthalmology and hepatology. Apart from being used to measure hepatic and cardiac function, it is applied in neurosurgical procedures.

Indocyanine green is composed of small particles that exhibit diffuse fluorescence when exposed to near-infrared (NIR) excitation light (λ = 600 – 900 nm) delivered by a dedicated optical system. The absorption spectrum of the tricarbonate green dye shows an excitation peak at λ_{Ex} = 805 nm and an fluorescence emission peak at λ_{Em} = 835 nm. Owing to the inherent property of ICG to emit light in the near-infrared spectral range, there is virtually no interferring background autofluorescence arising from the main components of blood (hemoglobin and water). The resulting tissue penetration depth that can be used for detection of NIR fluorescence ranges from 0.5 cm – 1.5 cm.[52,53]

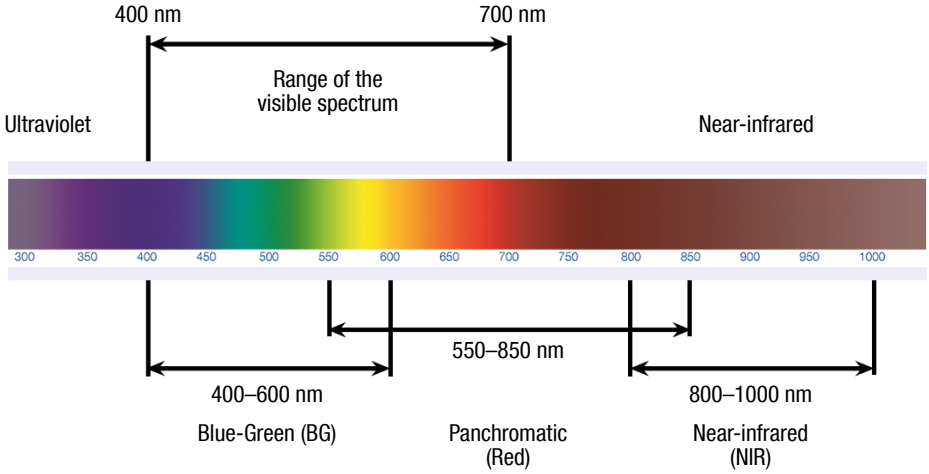
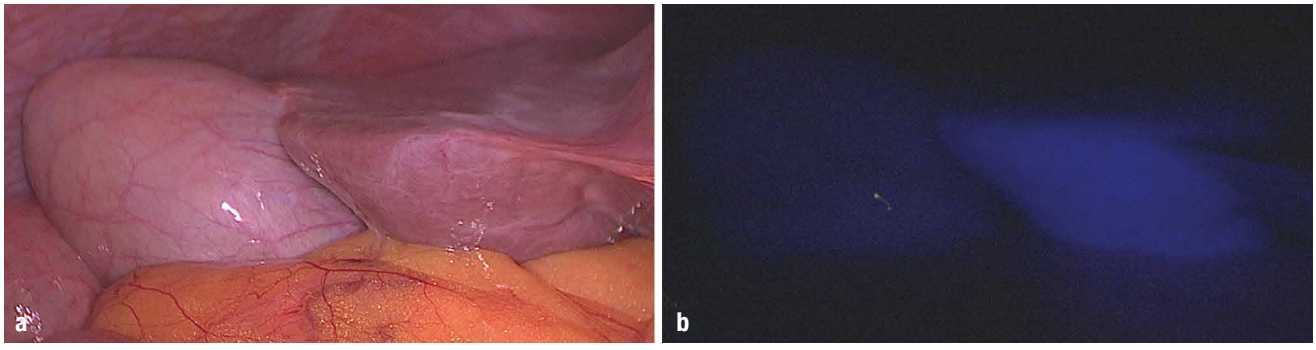


Fig. 1.2 Electromagnetic spectrum with close-up view on the visible and near-infrared wavelength ranges.

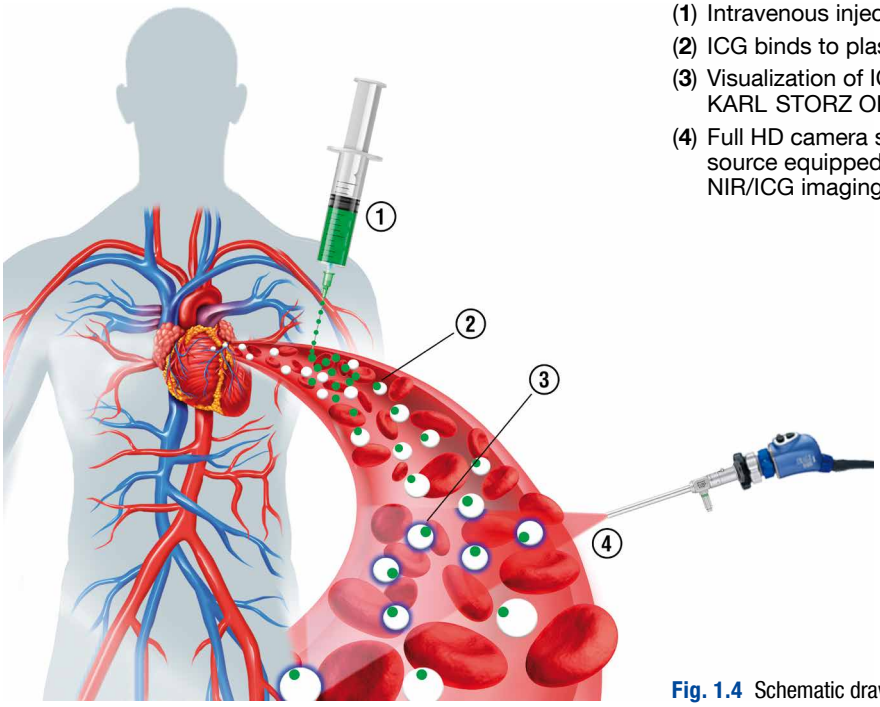
After intravenous injection, ICG binds to plasma proteins causing the agent to be confined within the intravascular space. The ICG protein complexes are then excreted in bile via the liver. The fluorescence of the bile can be used for real-time visualization of the extrahepatic bile ducts during near-infrared fluorescence cholangiography (NIR-FC).



Figs. 1.3 Excretion of ICG from the liver. Intraoperative views taken during white light mode (**a**) and NIR/ICG mode (**b**).

Following submucosal injection, ICG is distributed in lymph where it binds to lipoproteins, and is drained via lymphatic pathways and nodes. In view of these characteristics, ICG lends itself to be used as a perfect marker for SLN mapping.

The use of indocyanine green ICG is associated with a low risk of adverse effects. The risk of allergic reactions is one out of 42.000. For safety reasons, the use of ICG is contraindicated in patients with insufficient liver function and in those allergic to substances containing iodine, which is incorporated in the agent to a small fraction.[25,40]



(**1**) Intravenous injection of ICG.
(**2**) ICG binds to plasma proteins.
(**3**) Visualization of ICG in bloodstream with the KARL STORZ OPAL1® technology for NIR/ICG imaging.
(**4**) Full HD camera system coupled to a Xenon cold light source equipped with a special filter required for NIR/ICG imaging.

Fig. 1.4 Schematic drawing showing intravenous administration of ICG.

1.3 Near-Infrared Imaging Technology

All of the video stills presented in this brochure were captured using KARL STORZ OPAL1® technology for NIR/ICG imaging, which can be operated in dual mode for both white light and ICG-enhanced NIR fluorescence imaging. Apart from full HD image quality in white light mode and backlight illumination with true color gamut, the system offers a high level of user-friendly functionality. Switching from standard white light mode to near-infrared mode is simply done via foot-pedal control. Visualization in both modes is improved by use of the KARL STORZ IMAGE1 S™, which comes with various imaging modules that can be selected according to surgeon's preferences. The KARL STORZ OPAL1® technology for ICG-enhanced NIR fluorescence-guided procedures is fully compatible for extended applications such as 3D imaging, flexible endoscopy, and open surgery procedures (Fig. 1.5). For additional information, see the addendum section of this brochure, page 20.

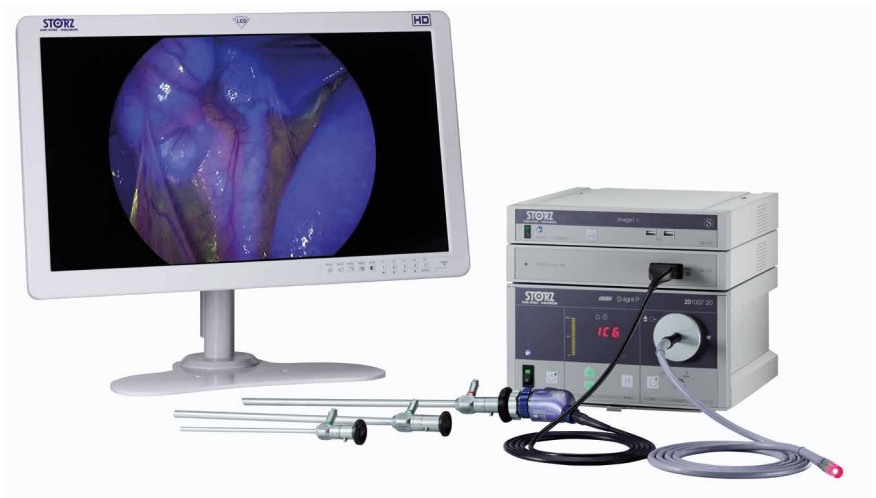


Fig. 1.5 The KARL STORZ OPAL1® technology can be operated in dual mode for both white light and ICG-enhanced NIR fluorescence-guided procedures.

2 Technique of SLN Mapping in Gynecology

2.1 SLN Mapping in Cervical and Endometrial Cancer

Based on the standard protocol applied at the authors' institution for the treatment of cervical and / or endometrial carcinomas, the tracer is injected intracervically in both procedures.[27,44] Following identification and removal of the SLNs, a radical or simple laparoscopic hysterectomy is performed, depending on tumor stage and other contributing factors.

Once general anesthesia has taken effect, the patient is placed in a dorsal lithotomy position with the arms tucked to the body. The patient is then prepped and draped. A preliminary examination is performed under anesthesia and a 10-mm umbilical incision is made using a # 11 scalpel blade. A Veres needle is inserted in the peritoneal cavity. Provided that proper placement of the needle has been confirmed with the routine safety maneuvers, a 25-mmHg pneumoperitoneum is established. Using a spezialized 30°-laparoscope (KARL STORZ Tuttlingen, Germany), equipped with a filter for optimal reproduction of ICG-enhanced NIR fluorescence, abdomino-pelvic organs and the peritoneal surfaces are inspected to rule out iatrogenic injuries that may have occurred during trocar insertion and to confirm the absence of extrauterine spread of disease.

At this stage of the procedure, the pneumoperitoneum pressure is lowered to 12 mmHg. A steep Trendelenburg position is adopted and three auxiliary trocars are introduced under direct laparoscopic vision, two of which are 5-mm trocars, placed in the right and left lower abdominal quadrants, approximately 2 cm medial and cranial to the anterior superior iliac spine, lateral to the inferior deep epigastric vessels. Finally, a 12-mm suprapubic trocar is placed in the midline.

Next, the ICG dye is injected in the cervical submucosa and deep into the stroma at the four quadrants of the cervix (Fig. 2.1a). To date, no consensus has been reached between the various centers as to the concentration and volume of the ICG solution to be injected, which is why the reported parameters may range from 1.25 mg/ml and 4 ml up to 5 mg/ml and 8 ml. The current practice at the institution of the authors is that one vial of 25 mg ICG powder (Pulsion®) is diluted in 10 ml of sterile water. A total volume of approximately 6 ml of ICG solution is administered to the four cervical quadrants, i.e., 1.5 ml per injection site (Figs. 2.1a–c).

Once the tracer has been injected as described, a uterine manipulator is placed. Prior to gaining access to the retroperitoneal space (Fig. 2.2), the camera system is switched to NIR/ICG mode to detect fluorescence which is emitted by lymphatic vessels or from an SLN. While still in white light mode, transillumination occasionally allows the green color of the ICG dye to be detected through the peritoneal lining. Commonly, once the NIR/ICG mode is activated, a clearly distinct fluorescent signal is noticeable (Fig. 2.3).

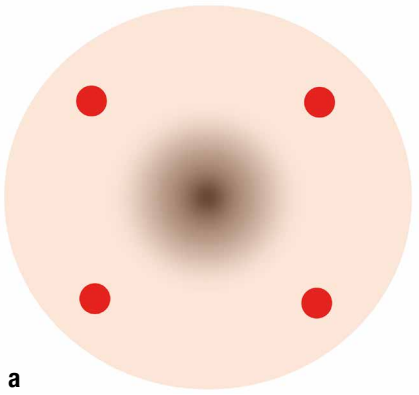
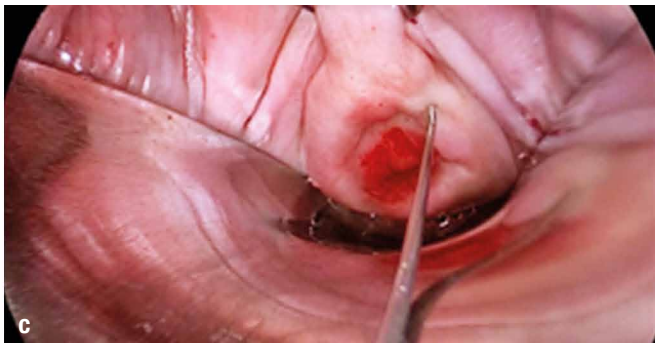


Fig. 2.1a Injection of 1.5 ml of ICG solution at each of the four cervical quadrants (●).



Figs. 2.1b-c The syringe is drawn up with the ICG solution (**b**). Intracervical injection of the tracer (**c**).

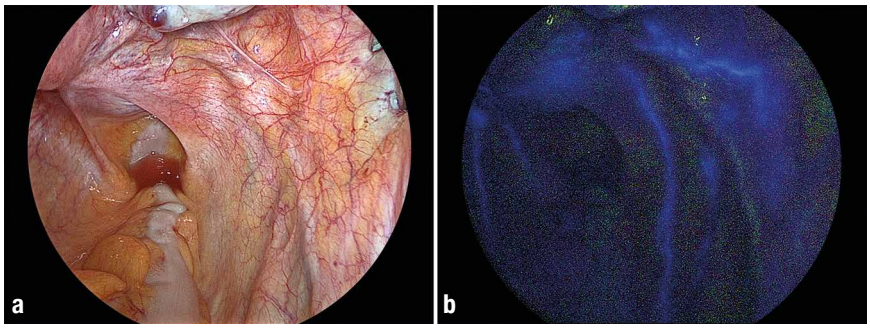


Fig. 2.2 Laparoscopic view (white light mode) of the pelvis after intracervical injection of the ICG dye.

Once the NIR mode has been activated via foot-pedal control, a distinct fluorescent signal is clearly observed before the peritoneum is incised to gain access to the retroperitoneal lymphatic tissue.

Note the two lymphatic pathways highlighted by fluorescence: an *upper paracervical pathway (UPP)*, running parallel to the uterine artery to reach the lymph nodes located on the pelvic side wall, and a *lower paracervical pathway (LPP)*, running along the mesoureter and draining to the lymph nodes located in the presacral area.

The peritoneum of the pelvic side wall is then opened to access the retroperitoneum. During this maneuver, the uterus is pushed upwards and toward the contralateral side to build up tension and to expose the anatomical site of interest. The pelvic peritoneum is then cut cranially, over the psoas muscle, parallel and lateral to the adnexa and the infundibulopelvic ligament (Fig. 2.4).

The infundibulopelvic ligament is medialized and the retroperitoneal areolar tissue is developed bluntly. The ureter is identified on the posterior leaf of the broad ligament and mobilized medially along with the adnexa.

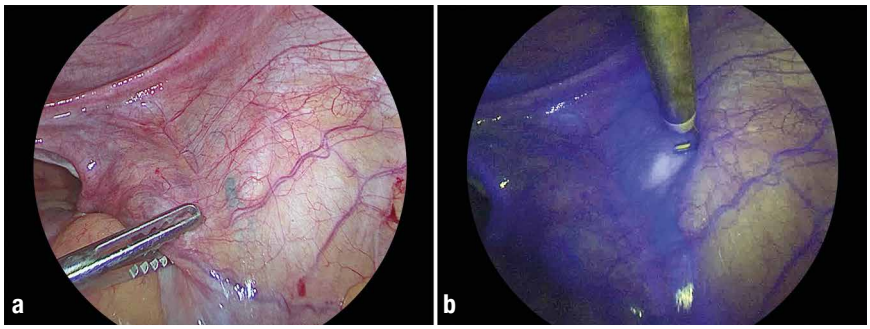


Fig. 2.3 A pale green color of the injected ICG dye is occasionally noticeable under white light mode.

After switching to NIR/ICG mode, a clearly distinct fluorescent signal is revealed.

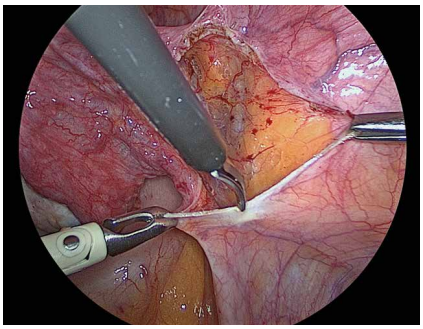


Fig. 2.4 The pelvic peritoneum is cut cranially, over the psoas muscle, parallel and lateral to the adnexa and the infundibulopelvic ligament, to gain access to the retroperitoneal pelvic space.

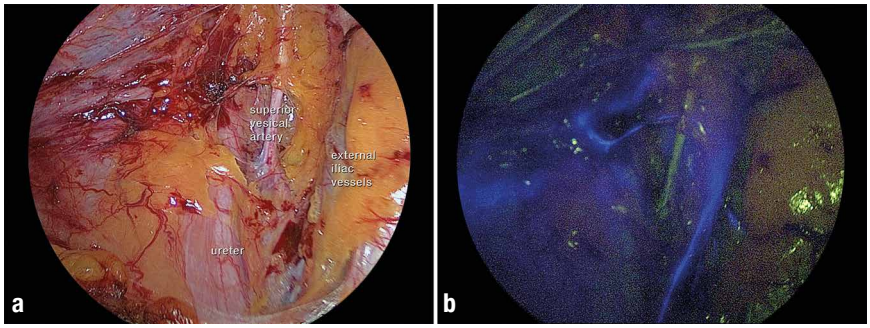


Fig. 2.5 The main retroperitoneal landmarks (*ureter, external* and *internal iliac vessels*) are easily identified through blunt dissection.

Switching to NIR/ICG mode allows the lymphatic vessels exhibiting fluorescence to be readily identified and followed to the SLN. Note the UPP running parallel to the uterine artery and draining to the lymph nodes located on the pelvic sidewall.

The iliac vessels are identified and the retroperitoneal space is dissected bluntly. Blunt dissection of tissue is of utmost importance in order to minimize the risk of inadvertent disruption of lymphatic vessels and ensuing spillage of ICG solution, resulting in impaired vision during NIR/ICG mode (Fig. 2.5).

Then, the camera system is switched to NIR/ICG mode to detect the SLN.

Inspection of the lymphoadipose tissue in the retroperitoneum is initiated in the paracervical area and proceeds laterally and cranially, following the anatomy of the cervical lymphatic drainage pathways. The parametrial tissue is inspected first, the tissue in the obturator fossa, along the external, internal and common iliac vessels, is examined subsequently.

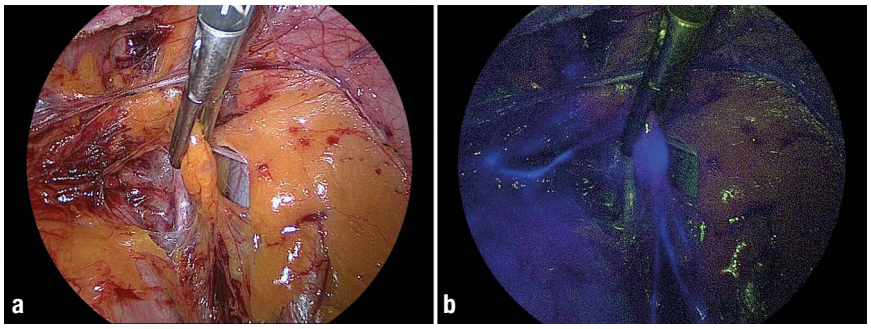


Fig. 2.6 Once the SLN has been identified, it is excised. Frequently, the SLNs are found lateral to the superior vescical artery and the ureter, medial to the external iliac vessels and ventral to the obturator nerve. Lymph nodes located in this region are also termed *Leveuf-Godard lymph nodes*.[35] Lymph nodes that drain the upper paracervical pathway are typically located here. The foot-pedal is used in a straightforward manner to toggle between NIR/ICG mode and white light mode. In this way, the operating surgeon is enabled to maintain control of the surgical site throughout this crucial stage of the prodecure and to double check the lymph node prior to its excision.

Once a lymphatic vessel has been identified by fluorescence imaging, one follows its course until the SLN is detected (Fig. 2.6).

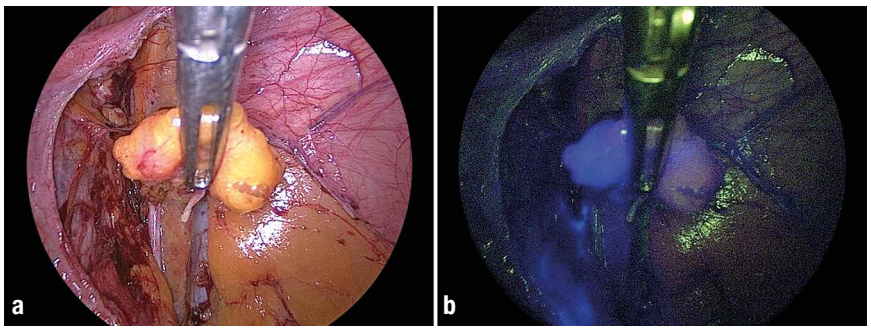


Fig. 2.7 Once the SLN is excised, the extracted specimen is sent for pathological analysis. Sentinel lymph nodes can be submitted to ultrastaging with immunohistochemistry staining. Toggling between NIR/ICG mode and white light mode allows to accurately identify and excise the sentinel lymph node.

The SLN is then excised, removed and sent for histopathological analysis (Fig. 2.7).

In patients treated for cervical cancer, an intraoperative frozen section analysis of the SLN is performed. Given a confirmed diagnosis of metastatic disease, the planned surgical procedure is aborted in favor of adjuvant chemotherapeutic or radiochemotherapeutic treatment. In patients suffering from endometrial cancer, the SLN is subjected to a thorough histopathological workup. The SLN is the first lymph node draining the cervix and is usually located lateral and dorsal to the external iliac vessels, medial to the superior vesical artery and ventral to the obturator nerve.

Less commonly, the SLN is located in the presacral area or along the course of the common iliac vessels. Additional lymph nodes detected by NIR/ICG fluorescence distal to the SLN are also removed labelled as echelon lymph nodes and sent for final histopathological assessment.

Not infrequently, the SLNs are located at uncommon anatomical sites. In these cases, the distinct fluorescent signal is also readily identified in NIR/ICG mode and allows to accurately perform SLN mapping (Figs. 2.8, 2.9).

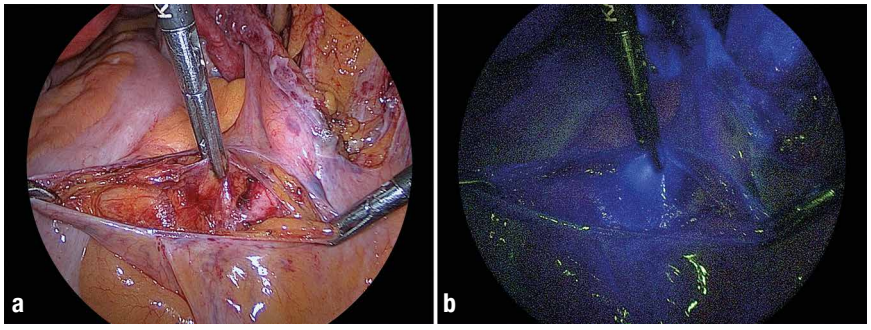


Fig. 2.8 Not infrequently, SLNs are found at uncommon sites. In this case, a presacral SLN draining the lower paracervical lymphatic pathway along the mesoureter is identified and excised. Sentinel lymph nodes located at less common sites can also be detected by the distinct fluorescent signal which is readily noticeable under NIR/ICG imaging.

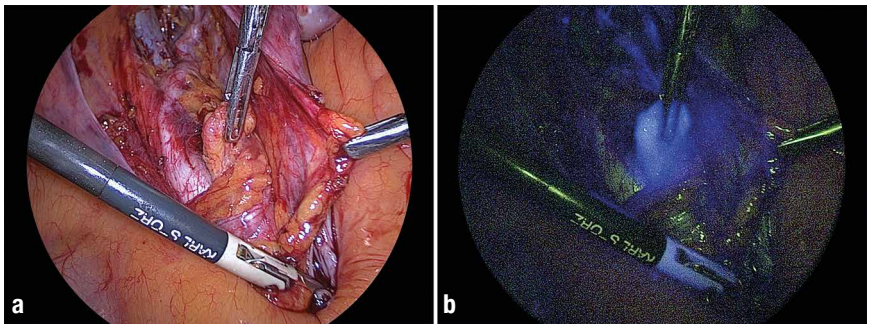


Fig. 2.9 An SLN draining the lower paracervical lymphatic pathway is detected medial to the common iliac artery and excised. Unlike SLN mapping with NIR/ICG imaging, the use of ^{99m}Tc requires a gamma probe to be inserted repeatedly via a 12-mm trocar. ICG-enhanced fluorescence-guided SLN mapping not only allows to work with all operating trocars, but also simplifies and expedites the procedure.

Four main lymphatic drainage pathways have been described for the uterus.[17,20]

- an *upper paracervical pathway* that runs in proximity to the uterine vessels and drains to the lymph nodes in the obturator fossa and along the course of the external iliac vessels;
- a *lower paracervical pathway* that follows the course of the mesoureter and drains to the presacral lymph nodes;
- an *infundibulopelvic pathway* that runs along the infundibulopelvic ligament to the high paraaortal lymph nodes located above the inferior mesenteric artery arteria mesenterica inferior, and
- a pathway that runs *along the round ligament* to the *inguino-femoral* and to *Cloquets' lymph nodes*.

Subject to the predominant lymphatic pathway, SLNs may be found in any of the anatomical areas described here.

By toggling between white light mode and NIR/ICG mode, the surgeon is enabled to maintain constant control of the surgical site and to double check the selected lymph node prior to its excision. The method eliminates the need to repeatedly insert a gamma probe through a 12-mm trocar, which is required when using ^{99m}Tc radiocolloid and therefore simplifies and expedites the SLN mapping procedure (Fig. 2.9).

Since metastatic lymph node involvement can adversely affect the accuracy of SLN mapping by tumoral occlusion of the physiologic lymphatic drainage, any macroscopically suspicious lymph node is excised as well. The planned surgical procedure (radical or simple hysterectomy) is then completed laparoscopically.

2.2 SLN Mapping in Vulvar Cancer

For non-endoscopic detection of ICG-enhanced NIR fluorescence, the authors use a dedicated optical device (VITOM® Exoscope, KARL STORZ Tuttlingen, Germany) which is attached to the operating table by a holder (Fig. 2.10). A total of 8 ml of ICG solution is injected in the peritumoral area both superficially and at a depth of about 1 cm (Fig. 2.11).

Ten minutes after tracer injection, the first lymphatic drainage can be detected by transcutaneous fluorescence.

At this stage of the procedure, a skin incision is placed parallel to the inguinal ligament and carried down to Camper's fascia. Once the fascia has been incised, the lymphoadipose tissue is developed bluntly. Care must be taken to preserve integrity of lymphatic vessels and to prevent undue leakage of the tracer, resulting in impaired fluorescence imaging compromising proper identification of the SLN. With the VITOM® Exoscope coupled to a spezialized video camera for NIR/ICG imaging, SLNs can be identified and removed selectively (Fig. 2.12, see overleaf).

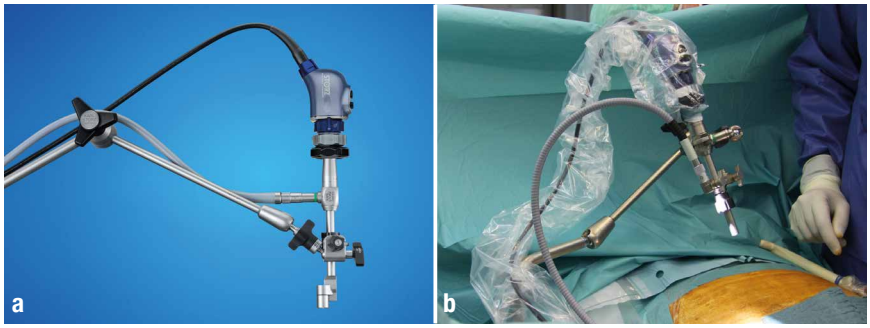


Fig. 2.10 VITOM® Exoscope for ICG-enhanced NIR visualization and standard white light imaging. The device is firmly fixed to the operating table.

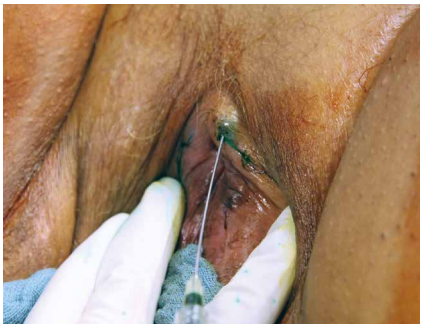


Fig. 2.11 Peritumoral injection of ICG solution.

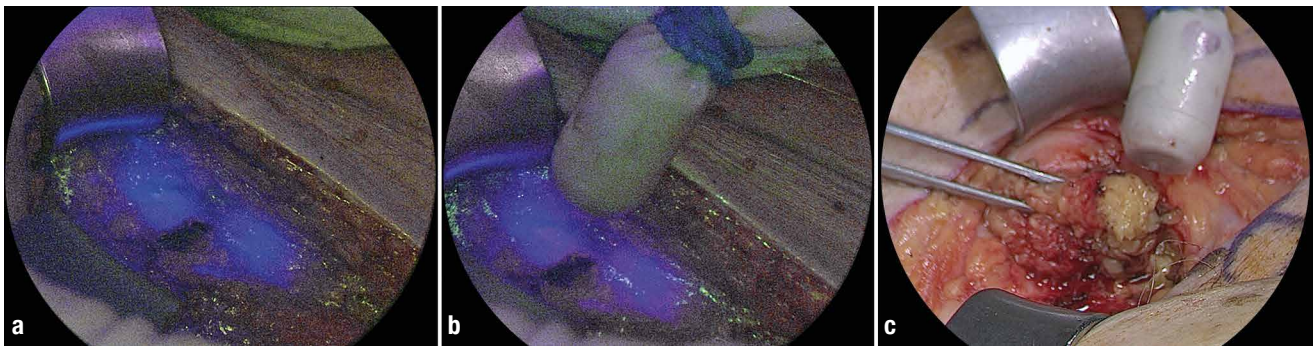


Fig. 2.12 Following peritumoral injection of ICG dye, the SLN is localized by NIR fluorescence which is clearly noticeable in the inguinofemoral triangle.

Using ^{99m}Tc radiocolloid in combination with NIR/ICG technology, the gamma probe is inserted to double-check and selectively confirm that the appropriate lymph node is being removed.

Same surgical site as shown in (**b**), but in white light mode.

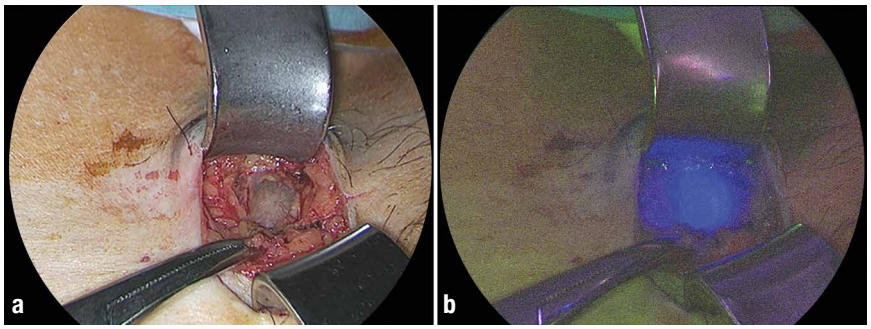


Fig. 2.13 Toggling between NIR/ICG mode (**b**) and white light mode (**a**) enables the surgeon to identify and double-check the selected SLN prior to its excision.

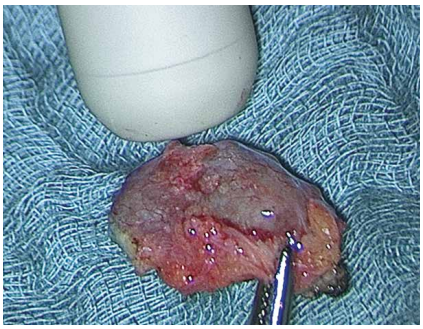


Fig. 2.14 Following excision, the extracted SLN specimen is sent for histopathological analysis.

Using ^{99m}Tc radiocolloid in combination with NIR/ICG imaging, a gamma probe is inserted to double-check the selected lymph node, making sure that the appropriate node is being removed (Fig. 2.12). Using the VITOM® system in NIR/ICG mode, the SLNs can be detected and removed selectively (Fig. 2.13) in an accurate and straightforward fashion. The excised specimen of the SLN is sent for histopathological analysis (Fig. 2.14).

3 Benefits and Limitations of the SLN Mapping Technique

The general concept of SLN mapping is not a new one. It is widely adopted as the current standard of care in the management of various gynecologic malignancies, including vulvar cancer.[59,60] Even though SLN mapping has been scientifically monitored and evaluated for more than ten years in the treatment of other malignant entities, such as cervical and endometrial cancer, it was the advent of ICG-enhanced NIR fluorescence imaging that only recently has contributed to a more widespread clinical acceptance. Among the most significant benefits afforded by SLN mapping are a potential reduction in the rate of needless systematic staging lymphadenectomies and associated morbidity, identification of lymph nodes in uncommon locations, and the option to make use of ultrastaging protocols.[42,55]

3.1 Cervix Carcinoma

Early stage cervical cancer is treated surgically with radical hysterectomy. In selected cases, a fertility-sparing approach with trachelectomy or extensive cervical conization is indicated. Since metastatic lymph node involvement remains the most important prognostic factor in both therapeutic options, it is mandatory that bilateral pelvic lymphadenectomy be performed. However, in most cases, the pelvic lymph nodes are negative for tumor involvement. In these patients, a routine systematic lymphadenectomy will result in prolonged duration of surgery, additional costs and an increase in the rate of intraoperative and long-term postoperative complications, such as bleeding, ureteral and nerve injury, lower-extremity lymphedema, lymphocele formation and sensory loss. Even though SLN mapping is still not considered an alternative option to systematic pelvic lymphadenectomy, it is frequently applied in routine clinical practice.[14] Given the prognostic significance of metastatic lymph node involvement in patients with cervical cancer, it is recommended that a therapeutic strategy be chosen in which all SLN are excised along with every lymph node suspected for metastatic infiltration, and that a systematic contralateral lymphadenectomy be performed in cases of unilateral SLN mapping.[12]

3.2 Endometrial Carcinoma

Based on a revision issued by the FIGO committee in 1988, surgical staging is recommended for endometrial carcinoma and should include an assessment of the pelvic and para-aortic lymph nodes. In view of the relatively low rate of metastatic infiltration of lymph nodes seen in the majority of patients on the one hand, and the morbidity associated with lymphadenectomy on the other hand, controversy remains as to whether there is a definite therapeutic value that outweighs the potential risks and adverse effects of the procedure.[5,6,32] To date, an *'all-or-none'* strategy has been widely used, where patients are triaged intraoperatively according to pathological risk factors determined on the basis of uterine frozen sections.[33,38] However, the results are suboptimal and fraught with a significant rate of both over- and undertreatment.[39,51] In the light of this context, SLN mapping represents a sensible and smart solution to the problem.[41,62]

Whenever SLN mapping / biopsy is adopted instead of complete lymphadenectomy, a SLN algorithm should be adhered to, which requires that all SLNs are excised along with any lymph node suspected for metastatic infiltration, and that a systematic contralateral lymphadenectomy be performed in cases of unilateral SLN mapping.[3]

Based on the NCCN* clinical practice guidelines in oncology issued in 2015, SLN biopsy is considered an adequate alternative to systematic lymphadenectomy in selected endometrial cancer patients. Even though the standard protocol employed by most centers stipulates that the tracer be injected intracervically, some authors advocate the use of hysteroscopic peritumoral injection to account for the fact that a tumor contained within the uterine corpus, unlike a cervically confined lesion, may exhibit an aberrant lymphatic drainage pattern.[15,36] However, to date, no significant differences have been shown between both techniques in terms of detection rate, negative predictive value and anatomic localization.

* *National Comprehensive Cancer Network*

3.3 Vulvar Carcinoma

In the past decades, surgical treatment of vulvar cancer has evolved from en bloc resection of the vulva and bilateral inguinofemoral lymphadenectomy by means of a longhorn incision to radical tumorectomy of the vulva with separate incisions for the groin lymph nodes, the so-called triple-incision technique, offering the benefit of reduced surgical morbidity. However, inguinofemoral lymphadenectomy is nonetheless associated with a high risk of postoperative lymphedema.[59] Even though numerous operative techniques have been proposed to reduce the rate of this sequela, the best option to be adopted in this case is SLN biopsy sampling.[30,37,59]

Based on the results reported in two large cohort studies, SLN biopsy is considered the current standard of care in the treatment of patients with vulvar cancer.[34,59] Most commonly, the procedure is performed with ^{99m}Technetium and blue dye. Proper detection of all sentinel nodes in the inguinal region is key to patient survival. For this reason, preoperative fusion imaging using *single photon emission computed tomography (SPECT)* and *CT* – termed *SPECT-CT* – is recommended because this hybrid modality has been found to significantly enhance the SLN detection rate.[4] Now, that a dedicated instrument set for ICG-enhanced fluorescence-guided SLN mapping is available on the market, an increasingly widespread acceptance of the technique including its use in the treatment of vulvar cancer, can be anticipated.

3.4 Comparison of Various Modalities of SLN Mapping

Historically, the first group of tracers used for SLN mapping was that of radiolabeled colloids, typically the Technetium isotope ^{99m}Tc. Depending on the protocol applied for administrating the tracer, ^{99m}Tc is injected between 20–24 hours ('long' protocol), 2–4 hours ('short' protocol) or intraoperatively ('ultrashort' protocol).[1,24]

In the authors' clinical practice, the use of a non-radioactive colored dye, such as ICG, is clearly preferred for several reasons. Following injection of the radiopharmaceutical, commonly done preoperatively in a protected environment (nuclear medicine department), the tracer is transported with lymph to the sentinel nodes where intraoperative detection is feasible with the interpretation of an audiometric signal generated by a handheld scanner with a gamma-sensor probe.[41] The method comes with the additional drawback that it lacks the emission of visible light.

In order to overcome these limitations, a lymphoscintigraphy or a SPECT-CT is performed preoperatively to detect the number and anatomic location of the SLNs.[16] The radiopharmaceutical ^{99m}Tc has a physical half-life of 6.01 h and decays almost completely 24 hours after injection. Strict adherence to the operating room timetable is required to prevent a delayed beginning of surgery as this can be detrimental to the success of SLN mapping. Apart from that, radioguided SLN mapping requires the gamma probe to be inserted first in the abdomen, leaving only two ports for the laparoscopic instruments. The need to compensate the lack of one operating port can make dissection more cumbersome and, for obvious reasons, the repeated insertion of the probe for SLN detection can lead to a prolonged duration of the procedure.

While potential adverse reactions have been identified with the use of blue dyes (such as methylene blue, patent blue and isosulfan blue), the risk profile of indocyanine green is excellent.[40] Blue dyes are easy to use since they do not require any dedicated equipment and they are based on a colorimetric signal which is easily detectable. However, blue dyes travel quickly through the lymphatic system to the SLNs from where they migrate further to echelon nodes. Typically, the SLN will be stained blue within 5 to 10 minutes from the injection, and will remain stained for approximately 30 minutes or a little longer. If the SLN cannot be identified promptly within this timeframe, there is a risk that it cannot be identified at all or that an echelon node, which has stained in the meantime, is taken for the missed SLN and biopsied instead. As already mentioned in chapter 1, rare but severe allergic reactions have been described in the literature.

ICG is a compound with an extremely safe toxicity profile.[40,45] The dye can be injected intraoperatively and does not require any adjunctive preoperative imaging. Unlike SLN mapping with ^{99m}Tc, which commonly needs to be injected without anesthesia on the day prior to surgery, followed by preoperative radiologic imaging, most patients perceive the quality of care to be higher when ICG dye is used.[8]

Similar to blue dyes, ICG travels rapidly through the lymphatic system to the SLNs from where the agent migrates downstream to reach the echelon nodes. Unlike with blue dyes, ICG accumulates in the SLN for a longer time, even after the adjacent downstream nodes have been identified by NIR fluorescence, and therefore time-dependency is not an issue for ICG-enhanced fluorescence-guided SLN mapping. Another helpful feature of the latter method is, that the fluorescent signal elicited by NIR illumination is typically very strong and easy to detect. Overall and bilateral SLN detection rates have constantly been reported to be higher when ICG-enhanced NIR fluorescence imaging is used instead of ^{99m}Tc and/or blue dyes.[7,9,18,22,23,26,48,50,54,58]

3.5 Effect of BMI on SLN Mapping

Obesity has been consistently shown to adversely affect detection rates in SLN mapping. Ironically, obese patients may be the ones who benefit the most from this procedure as they have intrinsic risk factors leaving them prone to lymphedema and an increased perioperative morbidity.[46]

In multiple series, it has been demonstrated that an increased body mass index (BMI) has been associated with a reduced bilateral SLN detection rate in endometrial cancer.[19,58] Interestingly, the adverse impact of an increased BMI on SLN detection rates seems to be attenuated when ICG is used as a tracer instead of other dyes.[19,58] The strong fluorescent signal emitted after exposure to light of the NIR spectrum is helpful in identifying the SLN in the rich lymphoadipose retroperitoneal tissue of obese and morbidly obese patients. For this reason, ICG is considered the tracer of first choice in obese patients who need to undergo SLN mapping.

3.6 Learning Curve

It is estimated that 20 to 30 laparoscopic procedures for SLN mapping are needed to build the expertise that it takes for a surgeon to achieve an adequate detection rate and acceptable false-negative rate.[31,43] Recently, the *Society of Gynecologic Oncology (SGO)* has issued a literature review with consensus recommendations which advocate to adhere to the guidelines of the *American Society of Clinical Oncology (ASCO)* for SLN mapping in the treatment of breast cancer and in endometrial cancer.[21,31] In order to check the detection rates and false-negative rates, the first 20 patients should undergo a systematic lymphadenectomy after completion of SLN biopsy. In low-risk patients with a small risk of lymph node metastasis, this number should be increased appropriately.

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The KARL STORZ OPAL1® Technology for ICG-Enhanced Fluorescence-Guided SLN Mapping in Gynecology

OPAL1® Technology for NIR/ICG

based on IMAGE1 S™ camera system

① **IMAGE1 S™**
- FULL HD image quality
- NIR/ICG fluorescence in standard mode or SPECTRA A* mode

② **NIR/ICG telescope and camera head**
- 3-chip FULL HD camera head with high resolution, high NIR light sensitivity
- telescopes for fluorescence excitation and detection; can be used for white light and fluorescence modes
- telescopes with various lengths and diameters

③ **D-LIGHT P light source (Xenon light source)**
- no additional security measures (vs. Laser)
- with enhanced background display

④ **Footswitch**
- fast switch between white light and fluorescence mode

⑤ **Autoclavable fiber optic light cable**
- light transmission in the white light and NIR spectral range

* *SPECTRA A:* **Not for sale in the U.S.**

It is recommended to check the suitability of the product for the intended procedure prior to use.

OPAL1® Technology for NIR/ICG

based on IMAGE1 S™ camera system

Camera system

IMAGE1 S CONNECT™
TC 200

Camera control unit

IMAGE1 S™ H3-LINK
TC 300

Light source

D-LIGHT P/ 201337 01-1
Spare lamp: **20**133028
lamp modul: **20**133725

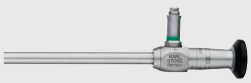
Camera head

H3-Z FI
TH 102

Light cables

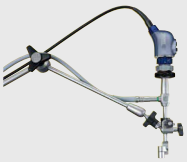
Fiber Optic Light Cables
495 NAC/NCSC/TIP/NCS/VIT

Telescopes



HOPKINS® Telescope
26003 ACA/BCA/AGA/BGA
26046 ACA/BCA

Open surgery



VITOM® II ICG
209160 25 AGA
Accessories:
28272 UGN/CN
28272 HC
28172 HR/HM

Laparoscopic Gynecology

Basic Set

26120 JL	VERESS **Pneumoperitoneum Needle,** with spring-loaded blunt inner cannula, LUER-Lock, **autoclavable,** diameter 2.1 mm, length 13 cm
2x 30103 GNG	**Trocar,** with blunt conical tip, with LUER-Lock connector for insufflation, size 11 mm, length 10 cm, color code: green
3x 30160 GNG	**Trocar,** with blunt conical tip, with LUER-Lock connector for insufflation, size 6 mm, length 10 cm, color code: black
33362 ME	**CLICKLINE Grasping Forceps,** rotating, dismantling, single action jaws, width of jaws 4.8 mm, with multiple teeth, for atraumatic and accurate grasping, with ratchet, without connector pin for unipolar coagulation, size 5 mm, length 36 cm
33362 ON	**CLICKLINE Grasping Forceps,** rotating, dismantling, single action jaws, with especially fine atraumatic serration, fenestrated, with ratchet, without connector pin for unipolar coagulation, size 5 mm, length 36 cm
33362 UM	**CLICKLINE Ovary Grasping Forceps,** rotating, dismantling, double action jaws, serrated, with ratchet, without connector pin for unipolar coagulation, size 5 mm, length 36 cm
33352 ML	**CLICKLINE** KELLY **Dissecting and Grasping Forceps,** rotating, dismantling, double action jaws, long, with ratchet, with connector pin for unipolar coagulation, size 5 mm, length 36 cm
33352 SN	**CLICKLINE** SCHNEIDER **Lymph Node Grasping Forceps,** rotating, dismantling, single action jaws, atraumatic, with ratchet, with connector pin for unipolar coagulation, size 5 mm, length 36 cm
34561 GS	**CLICKLINE Spoon Forceps,** rotating, dismantling, single action jaws, without ratchet, without connector pin for unipolar coagulation, size 5 mm, length 36 cm
34361 EH	**CLICKLINE Hook Scissors,** rotating, dismantling, single action jaws, without ratchet, without connector pin for unipolar coagulation, size 5 mm, length 36 cm
34351 MA	**CLICKLINE Scissors,** rotating, dismantling, double action jaws, serrated, spoon-shaped, without ratchet, rotating, dismantling, insulated, with connector pin for unipolar coagulation, size 5 mm, length 36 cm
38651 ON	**ROBI Grasping Forceps,** CLERMONT-FERRAND model, rotating, dismantling, with connector pin for bipolar coagulation, with especially fine atraumatic serration, fenestrated jaws, double action jaws, size 5 mm length 36 cm
38651 MD	**ROBI** KELLY **Grasping Forceps,** CLERMONT-FERRAND model, rotating, dismantling, with connector pin for bipolar coagulation, especially suitable for dissection, double action jaws, size 5 mm, length 36 cm, color code: light blue
38651 ML	**ROBI** KELLY **Dissecting and Grasping Forceps,** CLERMONT-FERRAND model, rotating, dismantling, with connector pin for bipolar coagulation, especially suitable for dissection, size 5 mm, length 36 cm
38651 MW	**ROBI** METZENBAUM **Scissors,** CLERMONT-FERRAND model, rotating, dismantling, with connector pin for bipolar coagulation, double action jaws, curved jaws, slender scissor blades, for cutting and bipolar coagulation, size 5 mm, length 36 cm
26173 BN	**Suction and Irrigation Tube,** with lateral holes, anti-reflex surface, with two-way stopcock for single-hand control, size 5 mm, length 36 cm
37370 GC	GORDTS and CAMPO **Coagulating Suction and Irrigation Tube,** bipolar, diameter 5 mm, length 36 cm, for use with suction and irrigation handles
30810	**Handle,** for suction and irrigation, **autoclavable,** for use with 5 mm coagulation suction tubes and 3 and 5 mm suction and irrigation tubes
26775 UF	**Coagulation and Dissection Electrode,** L-shaped, with connector pin for unipolar coagulation, size 5 mm, length 36 cm
30675 ND	**High Frequency Needle,** for splitting and coagulation, insulated, retractable, with connector pin for unipolar coagulation, size 5 mm, length 31 cm
2x 26005 M	**Unipolar High Frequency Cord,** with 5 mm plug for AUTOCON®, length 300 cm
2x 26176 LE	**Bipolar High Frequency Cord,** length 300 cm
39301 C	**Plastic Container for Sterilization and Storage of two Telescopes,** perforated, with transparent lid, with silicone telescope holder, external dimensions (w x d x h): 520 x 90 x 45 mm, for laparoscopy telescopes size 10 mm or similar
39301 CHS	**Silicone Telescope Holder,** for two rigid endoscopes up to diameter 10 mm, for Plastic Container 39301 AS/BS/CS
30173 LAR	KOH **Macro Needle Holder,** dismantling, with ergonomic handle, axial, disengageable ratchet, ratchet position right, jaws curved to left, with tungsten carbide inserts, diameter 5 mm, length 33 cm
30173 RAL	KOH **Macro Needle Holder,** dismantling, with ergonomic handle, axial, disengageable ratchet, ratchet position left, jaws curved to right, with tungsten carbide inserts, diameter 5 mm, length 33 cm
26168 Z	KECKSTEIN **Uterine Manipulator**