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Sentinel Node Mapping in Gynecologic Cancers: A Comprehensive Review

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Gynecologic cancers are one of the most important causes of women death worldwide. The sentinel lymph node concept was introduced by Cabanas in 1977 for the penile cancer. This technique was proven safe and feasible in selected cancers such as breast cancer, melanoma, or some gynecologic cancers. Sentinel lymph node mapping is increasingly used in early stages of cervical or vulvar cancer in particular due to the safety, high detection rate, and sensitivity of the technique. In this review, we will discuss in depth the most recent evidence of nuclear medicine and other techniques used to determine the status of the sentinel lymph node in women affected by gynecologic neoplasms. Although significant efforts have been already done in order to address several issues, there are still determined questions without a clear answer, in particular for endometrial, ovarian, and vaginal neoplasms.

Gynecologic neoplasms are one of the most common cancers worldwide and one of the most important causes of women death, in particular in low-income countries.[1] A recent worldwide analysis showed that in 2018, more than 12% of all tumor deaths were related to gynecologic cancers in woman, and more than 14% of all new cancers were found in the female reproductive system.[1] The most important are cervix uteri neoplasms and ovarian cancers both as incidence and mortality. Endometrial cancers (EC) show a significant incidence while other gynecologic neoplasms such as vulvar and vaginal, as well as melanoma localization in the reproductive female system are rarer.[1]

The staging of these cancers, essential in order to provide the best management, is based on the evaluation of the primary tumor, on the lymph node (LN) status and in the search of distant metastases.[2] However, in this context, the LN status is crucial given the prognostic and therapeutic impact of the presence of LN dissemination (LND).[3] In fact, in early stages, the radical surgery is the treatment of choice, and the sentinel LN (SLN) pathologic examination has gain increasing importance in order to establish the nodal status.

The SLN concept was introduced by Cabanas in 1977 for the penile cancer as the first regional LN that directly drains the lymph from the primary tumor.[4] This technique was proven safe and feasible in selected cancers such as breast cancer, melanoma, or some gynecologic cancers.[5] In the later in fact, it were Levenback et al who introduced this method in vulvar cancer in 1994[6] and since then, the SLN status determined by nuclear medicine techniques (using [^{99m}Tc]-labeled colloids with preoperative scintigraphy), vital dye or more recently fluorescent dye have become an irreplaceable modality for some gynecologic tumors, while for others, in-depth clinical studies are still needed for further elucidations.

The diffusion of this modality is based on the assumption that the presence or absence of tumor in the SLN is representative for the whole LN area and on the increased interest of the surgeons to propose minimal invasive techniques, in order to avoid surgical morbidity without impacting the efficacy of the surgical staging.[7] Furthermore, given the required interaction between several professionals in order to ensure an optimal management of several procedures, it has been suggested by several authors the need of an experienced team and of an adequate learning curve.[8-10]

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Recent international guidelines[11] have proposed a structured view of different issues, in particular for the nuclear medicine field in order to establish the (peritumoral or not) injection procedure, the typology of colloids, the type and time interval of images collection, type of images acquisition (planar lymphoscintigraphy and/or SPECT), procedures in surgery room, as well as interpretation criteria, in particular whenever a SLN is not detected, as well as radiation dosimetry issues for the patient and staff.

Although significant efforts have been already done in order to address several issues, there are still determined questions without a clear answer, such as the patient selection, the preoperative imaging, the needed learning curve, the treatment of recurrences, or the management of nodal micrometastases.[11,12]

Therefore, the aim of this review was to discuss in depth the most recent evidence of nuclear medicine and other techniques used to determine the status of the SLN in women affected by gynecologic neoplasms.

Vulvar Cancer

Vulvar cancer is a quite rare neoplasm (1% of all cancers in women and until 5% of all gynecologic cancers), although it is much more frequent in older women.[3] The most frequent histotype is the squamous cell carcinoma with almost 90% of all cases, often developed after human papillomavirus infection, while the other histologic types such as the Bartolini gland adenocarcinoma, basocellular carcinoma, malignant melanoma, or other sporadic histotypes represent roughly the remaining 10%.[3]

Distant metastases are very rare, while until 30% of patients could show LND at staging.[7] In fact, the LN status is the most powerful prognostic factor; overall survival at 5 years' patients dramatically drops from 90% in N0 to 50% in N+.[3,13] In the same time, LNs status determines the treatment given that in presence of metastatic groin LN, groin lymphadenectomy is needed; however, postsurgical morbidity is disturbing, in particular wound breakdown, infection, or chronic lymphedema.[14]

The lymphatic spread of vulvar cancer is observed first in homolateral superficial inguinal LNs[14] (Fig. 1), then in deep femoroinguinal LNs. Furthermore, although pelvic LNs can be metastatic, they are secondary to inguinal nodes dissemination. While in case of midline or almost midline lesion (<2 cm from midline), a bilateral lymphatic spread is possible (Fig. 2), and in case of lesions close to the clitoris, inguinal bilateral lymphatic drainage could be associated to pelvic spread.[2,15]

In this context, the sentinel node biopsy is a standard of care in early stages of vulvar cancer without clinical LND in order to reduce the postsurgical morbidity,[11] although some concerns have been raised by a case report showing the spread of cancer cells from metastatic LNs to contiguous dermis. The authors wonder about the role of sentinel node detection in case of already known increased inguinal LNs given that the retrograde flow of cancer cells in lymphatic channels could explain, by the high lymph flow promoted after the injection of colloids, the dermis dissemination.[16]

In the last two decades, several studies have shown the diagnostic impact, changes in the management, cost analysis, and the prognostic value of sentinel node detection followed by the biopsy in patients surgically treated for vulvar cancer. Few years ago, a systematic review and a meta-analysis of the

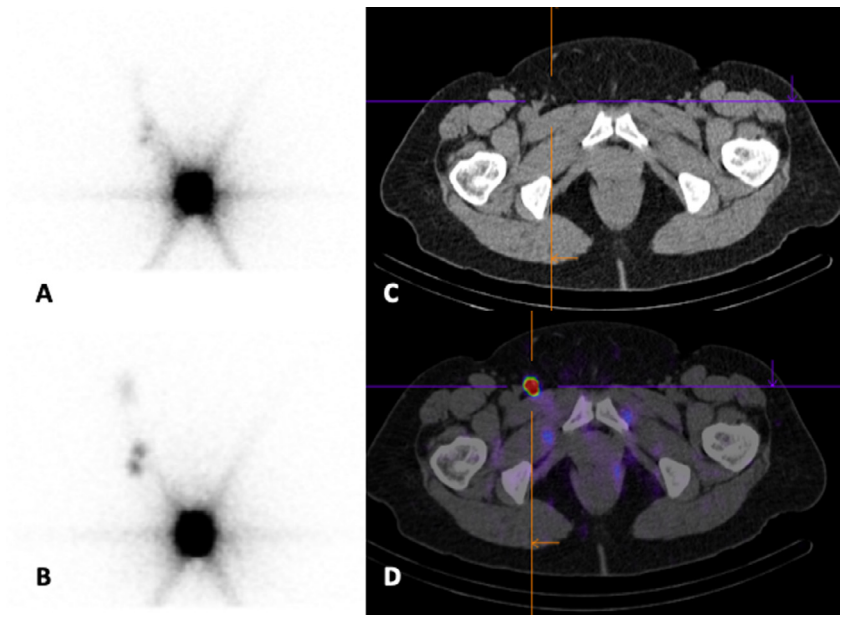

Figure 1 A 53-year-old woman, before surgery for vulvar carcinoma, underwent sentinel LN scintigraphy after injection of about 40 MBq of ^{99m}Tc nanocolloid in two peritumoral points, followed by planar images acquisition at 30 minutes and 150 minutes (A and B). Two focal uptakes were observed in planar acquisitions while the SPECT/CT (C-axial view of CT, D-axial view of SPECT/CT fusion) localized the uptakes in two sentinel millimetric right inguinal LNs. Surgery of the right hand side vulvar carcinoma and of right groin sentinel nodes allowed to stage the patient in pT1b N0.

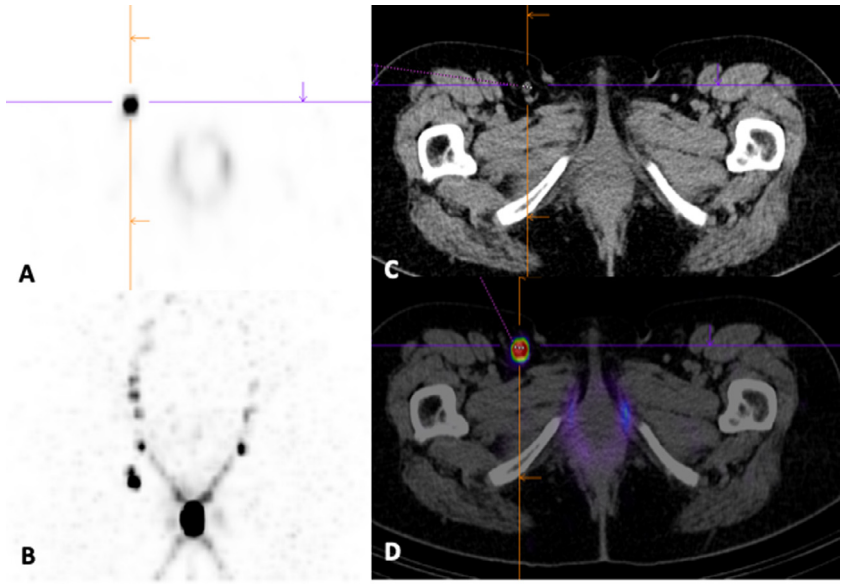

Figure 2 A 63-year-old woman, before surgery for vulvar carcinoma, underwent sentinel LN scintigraphy after injection of about 40 MBq of ^{99m} Tc nanocolloid in two peritumoral points, followed by planar images acquisition (not shown). Several focal uptakes were observed in planar acquisitions while the SPECT/CT (A-axial view of SPECT, B-MIP, C-axial view of CT, D-axial view of fusion) localized the uptakes in two sentinel millimetric bilateral inguinal LNs. During surgery, three sentinel LNs were harvested on the right groin, all negatives, and one in the left groin, negative as well.

literature showed pooled values of detection rate, sensitivity, and negative predictive value (NPV) of sentinel node biopsy in squamous cell vulvar carcinoma. The authors analyzed studies that had explored the role of the scintigraphy, but also studies using blue dye or fluorescent dye such as indocyanine green (ICG). Overall, in 33 studies, pooled patient and groin basis sentinel node detection rates were 94.4% and 84.6%, respectively. Overall, in 27 studies, pooled patient and groin basis sensitivity were 92% and 92%, while pooled NPVs were 97% and 98% for patient and groin basis analyses, respectively. However, the heterogeneity of the included papers was also pointed out, given that the mapping techniques were not homogenous (radioactive colloid vs blue dye vs fluorescent dyes), as well as the selection of patients. In fact, in some studies, clinical status of groin LNs was not evaluated prior to sentinel node detection, increasing the false negative rate due to the replacement of the invaded LN structure by tumoral cells and the blockage of lymphatic spread. Furthermore, the quality level of the included studies was not homogenous, although clustered analysis, based on quality, showed similar data. Last, publication biases were also detected, although probably not impacting the overall accuracy data.[17]

Moreover, in these decades of using the sentinel node detection in vulvar cancer, several issues have been explored in depth. First of all, the accepted to date indications are patients with FIGO stages IB and II, in case of unifocal tumor, greater dimension <4 cm and without any evidence of LND during the preoperative staging.[11,18,19] In a national study, it was showed that patients were best suited to SLN detection if they had a simple punch biopsy before surgery, rather than previous excision biopsy or excision tumor.[20]

Another issue extensively treated has been the preoperative imaging in order to clinically detect metastatic LNs; however, generally speaking, there are no imaging techniques with an optimal sensitivity. Recently, [^{18}F]FDG-PET/CT has shown a deceiving patient-based sensitivity of roughly 50% and 53% on groin-based analysis; furthermore, even in this context with a high rate of negative LNs, the total accuracy was lower than 75% on patient- and groin-based analysis.[21] Morphologic imaging techniques have also been explored, such as MRI, although showing a good specificity and interobserver agreement, reported sensitivity has been almost 50%,[22] insufficient in this context. Then, ultrasonography, although generally speaking, has a relatively good accuracy for the evaluation of inguinal area, but has shown a suboptimal sensitivity in vulvar cancer.[23] Therefore, to date, no imaging modality could replace surgical LN staging; however, given the relatively good specificity of all of the cited techniques, they could be used to select patients prior to sentinel node detection.[24]

In fact, the crucial issue in case of negative sentinel node is the efficacy of the surgical treatment; one paper did not observe any significant recurrence differences (P= 0.8) in patients undergoing SLN detection with lymphadenectomy in case of positive nodes compared to systematic lymphadenectomy.[25] Furthermore, several studies showed that when lymphadenectomy was omitted in case of negative SLN at pathologic ultrastaging, short-term (wound breakdown, cellulitis) and long-term (recurrent erysipelas, leg lymphedema) morbidities were significantly lower compared to patients undergoing lymphadenectomy, while groin recurrence was very low (2.3%), what is more, confirmed in a recent meta-analysis of the available literature.[26] Three-year survival rate was also excellent (97%), what is more, confirmed in a recent multicenter study.[3,27-33] Last but not least, several papers have shown the undebatable preferential choice of the patients for this method if the risk of

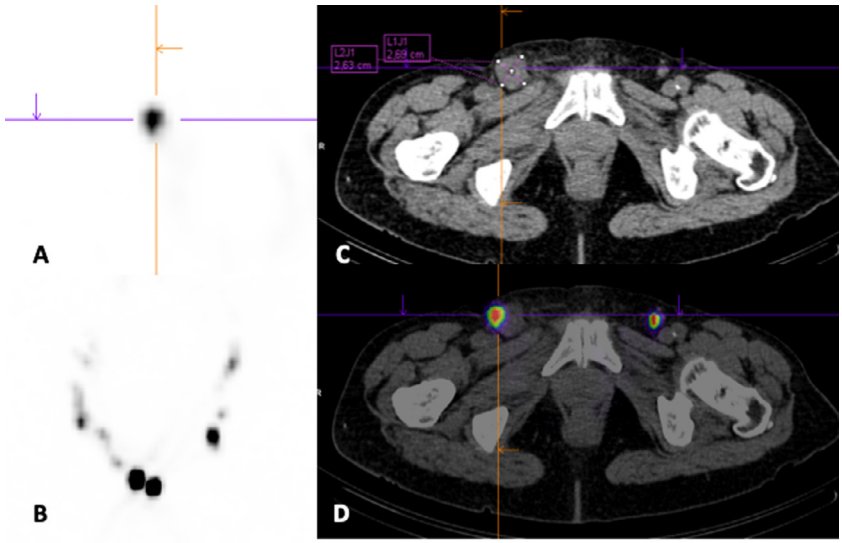

Figure 3 An 83-year-old woman, before surgery for vulvar melanoma, underwent sentinel LN scintigraphy. After injection of about 40 MBq of ^{99m} Tc nanocolloid in two peritumoral sites, planar images and SPECT/CT were acquired (A-axial view of SPECT, B-MIP, C-axial view of CT, D-axial view of fusion). Several focal uptakes were observed in SPECT/CT, noteworthy the right inguinal sentinel LN was measured 27 × 26 mm and was highly suspect for metastatic dissemination, it was confirmed at pathology, while two left millimetric inguinal LNs were not metastasized.

metastatic SLN is really low, given the overall negative impact of lymphadenectomy.[34,35]

Recently, several studies have stressed the cost-effectiveness and cost-utility analysis of SLN-based management (in one study associated to a 3-year follow-up) compared to inguinofemoral LN dissection,[36-38] showing and confirming the superiority of the sentinel node approach both in terms of costs and quality of life.

Another interesting explored issue has been the size of the sentinel node metastases, in fact this feature is also correlated with thorough pathologic examination because of equivocal data have been described about the impact of ultrastaging hematoxylin and eosin staining vs immunohistochemical staining.[20,39-41] Anyway, its implication on the management of these patients is clear given its correlation with the rate of nonsentinel nodes metastases and disease-specific survival.[42] Hopefully GROINSS VII will show, in the near future, the role of radiation treatment in groins with LNs metastases <2 mm,[43] while GROINS VIII will try to answer the question how to handle with lymphatic metastases >2 cm.[44]

Although several studies have explored the role of sentinel node scintigraphy before surgery of primary vulvar cancer, there are few studies that had the aim to evaluate sentinel node detection and its accuracy after primary surgery of the cancer or after excision biopsy. These studies have shown similar performance compared to the detection of sentinel node during the primary surgery.[45-47] However, the detection of the SLN appeared technically more challenging.[48,49]

Given that the squamous cell carcinoma is the commonest neoplasm of the vulva, the majority of the studies have targeted this histotype. Vulvar melanoma is the second commonest histotype, but only few studies and case reports have tried to show that SLN is a feasible technique in order to avoid futile postsurgery morbidity[50-53] (Fig. 3).

Finally, as well as in other gynecologic cancers, first studies using [^{99m}Tc]-labeled colloid to detect SLN were based on planar scans, but more recent studies using SPECT or SPECT/CT showed the highest detection rate and accuracy of this technique associated to the personalization of the lymphatic mapping and its impact in the adequate surgical planning of the groin.[54] Furthermore, another imaging modality has combined in one instrument the mobility of the gamma probe and the 3D presentation of SPECT, leading to the successful use of "SPECT freehand" in several neoplasms surgeries, among which vulvar cancer.[55] Last, efforts have been done in order to have a multimodal marker of the SLN in order to add the advantages of two modalities: radioactivity and fluorescence. In fact, in several cancers, this approach has shown its feasibility,[56] and particularly for vulvar cancer "the best of both worlds" has shown an excellent detection rate.[57]

In conclusion, the role of SLN scintigraphy is well established because it is feasible and safe, it allows to avoid futile postsurgery morbidity without increasing the recurrence rate and without impacting the overall survival. To date, SPECT/CT is the widespread modality of collecting images after an accurate selection of early stages, cN0, unifocal lesion <4 cm patients, taking care of the lesion localization in order to explore ipsilaterally or bilaterally the groin exploration, if the lesion is located in midline or near to midline.

Cervical Cancer

Cervical cancer is the fourth most common cancer in women, with an estimated number of incident cases of 569,847 patients in 2018[1]), usually related to human papillomavirus infection. It remains a relatively high mortality cancer, despite the fact that it can be detected quite easily by smear

or biopsy, this being mostly due to the unequal frequency of vaccination and screening among the different countries.

Early and adapted therapeutic management is crucial and special attention is given to LN involvement, as LN metastasis is one of the main prognostic factors in this disease, noticeably for the early-stage cancer.[58,59] More than the different histotypes, the nodal status in these groups of patients may impact the therapeutic choices, with radical surgery avoidance in case of pelvic LN invasion, or by eventually adding adjuvant therapy.[60]

Originally explored by pelvic and para-aortic lymphadenectomy, the nodal staging is now increasingly being realized by SNL mapping. Indeed, early-stage cervical cancers have a relatively low incidence of LN invasion, with a rate of 0%-8% in stage IA, 0%-17% in stage IB, 12%-27% in stage IIA, and 25%-29% in stage IIB[61]—according to the FIGO 2009 classification—[62], and a systematic LN dissection increases the risks of presenting complications such as vessel and nerve injuries, ureteral wound, infection, lymphocele, or chronic lymphedema.[63]

With the new integration of pelvic and para-aortic LN metastases in the FIGO 2018 classification,[64] imaging techniques like MRI or [^{18F}]FDG-PET/CT can now be used, with relatively good specificity, but with a lack of sensitivity.[65] In fact, given the relatively high specificity, these imaging techniques may be used to exclude from sentinel node mapping patients with clinically metastatic LNs. To date, the SLN mapping indications are therefore based on the former FIGO 2009 classification.[62] Nevertheless, these indications remain globally similar between the different guidelines, as the latest National Comprehensive Cancer Network (NCCN) guideline[66] recommends—similarly to the ESGO-ESTRO-ESP 2017 guideline[67]—the possibility to perform SNL mapping for these early stages of cervical cancers: IA1 with lymphovascular space involvement, IA2, IB, and IIA, with only IB1 and IIA1 considered for the NCCN, avoiding SNL mapping in patients with tumors>4 cm.[68]

Moreover, it has recently been shown that surgical assessment of the para-aortic LNs in patients with early-stage cervical cancer may be safely omitted. Indeed, del Carmen et al,[69] Lennox et al,[70] and Salvo et al,[71] demonstrated with retrospective cohort patients that lymphadenectomy does not confer survival advantage and that SLN mapping may allow accurate detection of LN metastases while reducing morbidity, even in case of para-aortic LN metastases. Further ultimate confirmation should be available with the prospective clinical trial SENTICOL III[72] and SENTIX.[73]

The usual lymphatic drainage areas for cervical cancers are the obturator or the external iliac region, with visible locations up to the para-aortic level,[74,75] and unusual drainage sites can be detected by the SLN mapping, such as presacral nodes.[76] It is worth noting the bilateral nature of lymphatic drainage of the uterine cervix, and the potential presence of multiple independent drainage pathways, which implies the need to perform a lateralized surgical lymphadenectomy in cases of unilateral SLN detection.[77]

The first multicentric study to validate the concept of SLN mapping in cervical cancers showed that previous pelvic lymphadenectomy, known parametrial or nodal invasion or previous pelvic radiation therapy, are exclusion criteria, while local surgery like cone biopsy or previous chemotherapy are not contraindications to perform SLN mapping.[78]

Current recommended procedures for injecting radiotracer are based to submucosal injections into the four quadrants of the cervix, with a volume of 0.5 mL per injection and an average activity of 110 MBq. For the biggest tumors, injection should avoid the tumoral necrosis, and postconization injection should be on the periphery of the scar. Since the average time of visualization of the SLN is within 2 hours, imaging can be performed in this time.[11] Dynamic lymphoscintigraphy study may be realized, but SPECT/CT slices are more informative due to a better localization of the drainage sites, and can lead to improve surgical approach[79] and decrease the intraoperative detection of the LNs.[80]

SLN detection can be carried out from 4 to 20 hours after the injection of the radiotracer, preferentially in laparoscopy. The whole procedure should also be performed by an experienced and trained team.[81]

Other benefits that SLN mapping could provide are the possibility to practice pathologic ultrastaging, and thereby identify micrometastases—defined as metastases ≤0.2 mm—and a fertility sparing-guided surgery like radical abdominal trachelectomy for young patients.[82,83]

Vital dyes and radiotracers were the first substances used to explore LN drainage (Fig. 4), with blue dye validated by Dargent et al[84] showing a detection rate of 89% and a sensitivity of 100%. Since the feasibility study of Plante et al,[77] Altgassen et al,[78] showed in the first multicentric study that the detection rate, sensitivity, and bilateral detection using combined techniques were higher than with one technique alone. Lecuru et al with the SENTICOL trial[85] confirmed a good detection rate of 97.8%, a sensitivity of 92% and a NPV of 98.2%. Roy et al[86] have also shown similar results with the combined techniques. It is interesting to note that 16.7% of patients presented a SLN located in aberrant sites, including 3.8% in the para-aortic area.

Two recent meta-analyses have confirmed these data: Tax et al[68] showed an overall and bilateral detection rate of respectively 94% and 72% with combined techniques, with an increase at 87% for the bilateral rate with tumor size <20 mm. Pooled sensitivity was 94% with ultrastaging and NPV ranged between 91% and 100%. Cheng-Yen Lai et al[87] found overall the same results, but these good overall results seem to be limited to early-stages cervical cancers, with a marked decrease in performance for locally advanced lesions, probably related to LN and lymphatic invasion that can impair drainage.[81]

Moreover, SLN mapping using radiotracer and blue dye with ultrastaging seems to be the most cost-effective strategy vs surgical lymphadenectomy, with respect to 5-year progression-free survival and morbidity-free survival.[88]

Recently, a new technique for SLN mapping using fluorescence dye and near-infrared fluorescence imaging has spread out. ICG is currently used in several countries and the only one for the moment to be approved by the FDA. It brings the possibility of real-time imaging with a nonirradiant, safe, and

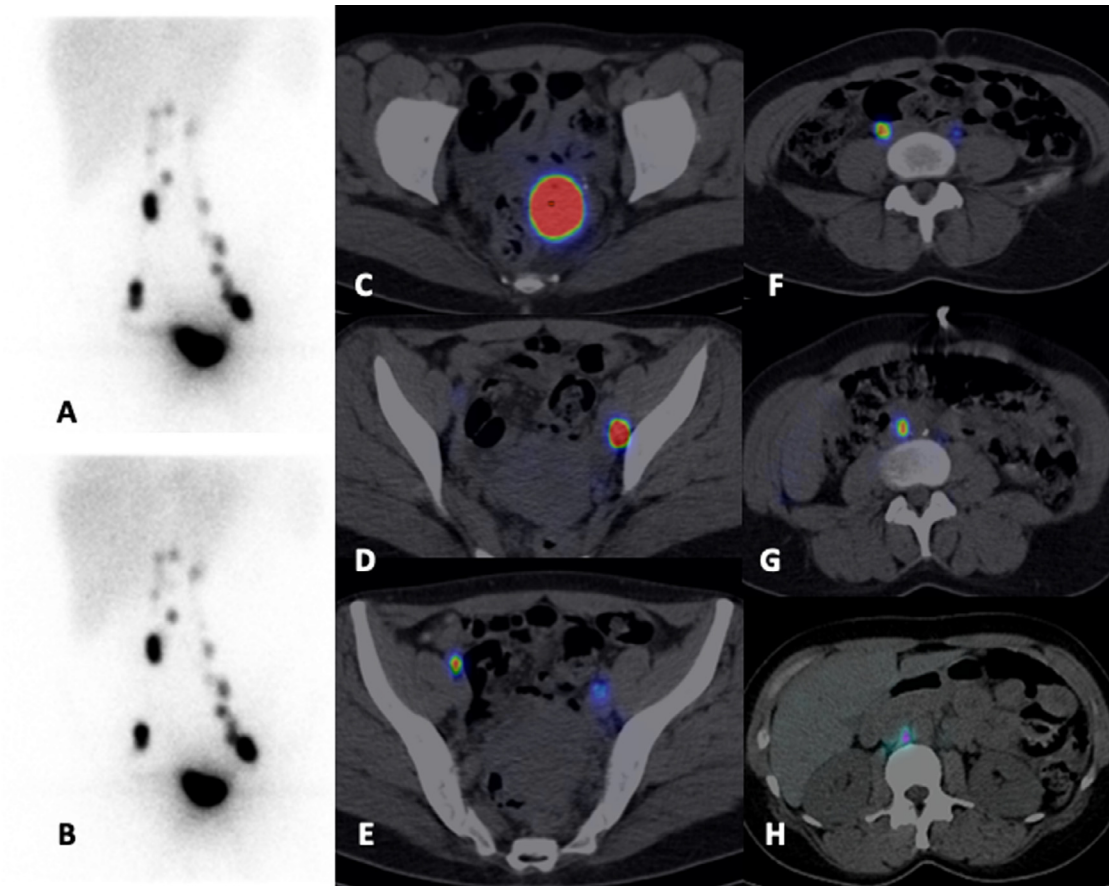

Figure 4 A 37-year-old woman with a FIGO IA endometrioid adenocarcinoma underwent sentinel lymph node scintigraphy. After four injections of about 40 MBq each, several focal uptakes were observed in planar acquisitions at 10 and 60 minutes (A and B). The fused SPECT/CT views showed the cervical injection site (C) and bilateral lymph node drainage with iliac external lymph node uptake (D and E). All nodes showed no metastatic spread.

reproducible technique. SLN can be visualized between the 5th minute and 1 hour after local injection into the cervix at the 3 and 9 o'clock positions[89] and seems to outperform the detection rate of the blue dye alone.[90] ICG mapping also seems to be superior in the detection rate to combined blue dye and radiotracer, especially in bilateral detection with a rate of 98.5% vs 76.3% and for tumors >2 cm.[91,92]

A recent meta-analysis from Ulain et al[93] confirms the significantly higher bilateral and unilateral detection with ICG detection rate, but with no difference in the overall detection rate (ODR) of SLN.

A combined technique with ICG and radiotracers like [^{99m}Tc]-labeled colloids has also been experimented, with good results, but remains to be confirmed later.[94] Other experimental techniques like optical fluorescence technology[95] or carbon nanoparticles[96] also require further studies.

What remains to be clarified is the management of the micrometastases, as their presence would decrease overall and recurrence-free survival,[97-99] but this has not been confirmed by the latest prognostic analysis of the SENTICOL trial.[100] According to the FIGO 2018 classification, their meaning is unclear; therefore, their presence as well as the one of isolated tumor cells may be recorded but does not change the stage.

To conclude the use of the sentinel node for early-stage cervical cancers is a high-performance, morbidity-limiting LN staging method, that can be performed with a combination of radiotracer and blue dye or ICG alone.

Endometrial Cancer

Endometrial cancer (EC) is the most common gynecologic malignancy in the developed countries, with a disease generally confined to the uterus at diagnosis (FIGO I).[101] In early-stage endometrial cancer, well or moderately differentiated endometrioid histotype (grade I or II), presents a favorable prognosis compared to grade III endometrioid histotype, and also papillary serous carcinomas, clear-cell carcinomas and carcinosarcomas which are at high risk of recurrence and metastases.[102,103] In 1987, Creasman et al showed that myometrial invasion and histologic grade were independent predicting factors for LN metastases.[104,105] Effectively, LNLN involvement occurs in approximately 10% in patients with stage I EC and the 5-year disease-free survival rate drops from 90% to 54% if LN metastases are present at the time of diagnosis.[106]

If combined pelvic and para-aortic lymphadenectomy remains relevant for patients with endometrial carcinoma of intermediate or high risk of recurrence (leading to an appropriate selection of patients for adjuvant therapy for adjuvant

therapy),[107] there is still no clear consensus between European and American oncologic societies in current treatment guidelines for low-risk endometrial carcinomas.[108-110] Abu-Rustum et al showed that direct para-aortic drainage in early stages of endometrial cancer is estimated to occur in only 1% of cases and especially when the tumor is localized in the uterine fundus (probably drains directly via the gonadal vessels).[111] Thus, depending on the localization of EC, SLN marking does not appear to be as easily achievable as in cervical or vulvar cancer due to the complex lymphatic drainage of the uterus,[112] which drains at the least to bilateral pelvic and/or para-aortic basins.

However, two European randomized trials (published in 2008 and 2009) concluded that routine systematic pelvic lymphadenectomy does not improve disease-free or overall survival while early and late postoperative complications were possible.[113,114] Hence, sentinel node mapping is increasingly being utilized for endometrial cancer staging, allowing in particular the detection of aberrant lymphatic drainage that would be missed on routine lymphadenectomy. Several studies and meta-analysis demonstrated that SLN biopsy plus side-specific LND, when SLN is not detected, is a reasonable alternative to a complete LND in early-stage endometrial cancers,[109,115-117] also including high-risk tumor histotypes.[118] Furthermore, Bogani et al underlined in a recent meta-analysis that sentinel node mapping is noninferior to standard LND in term of detection of para-aortic nodal involvement and recurrence rates (any site and nodal recurrence).[119]

There are four reported techniques injection leading to different results in term of SLN detection: cervical injection, endometrial peritumoral injection assisted by hysteroscopy, myometrial/subserosal injection, and more recently isthmocervical injection.[120-122] Obviously, cervical injection is the easiest approach (performed periorificially, as for cervical cancer, into the four quadrants), allowing the use of radioisotope the same day or 1 day before surgery.[11] In a meta-analysis of 26 studies, Kang et al showed that cervical injection was not inferior to other methods.[123] According to Sahbai et al, pericervical injection leads to significantly better ODR of SLN on SPECT/CT comparing to peritumoral injection (83% vs 69%, $P = 0.049$) while reducing invasiveness of the injection procedure.[124] About the rare risk of direct para-aortic drainage from the fundus, Abu-Rustum et al suggest that SLN detection could be improved by injection around the tumor or into the subserosal myometrium rather than into intracervical space.[111]

Concerning detection techniques, the majority of studies have used a combination approach. Indeed, the injection of [^{99m}Tc]-labeled colloid with nuclear imaging and/or intraoperative gamma counters (Fig. 5) is historically used in

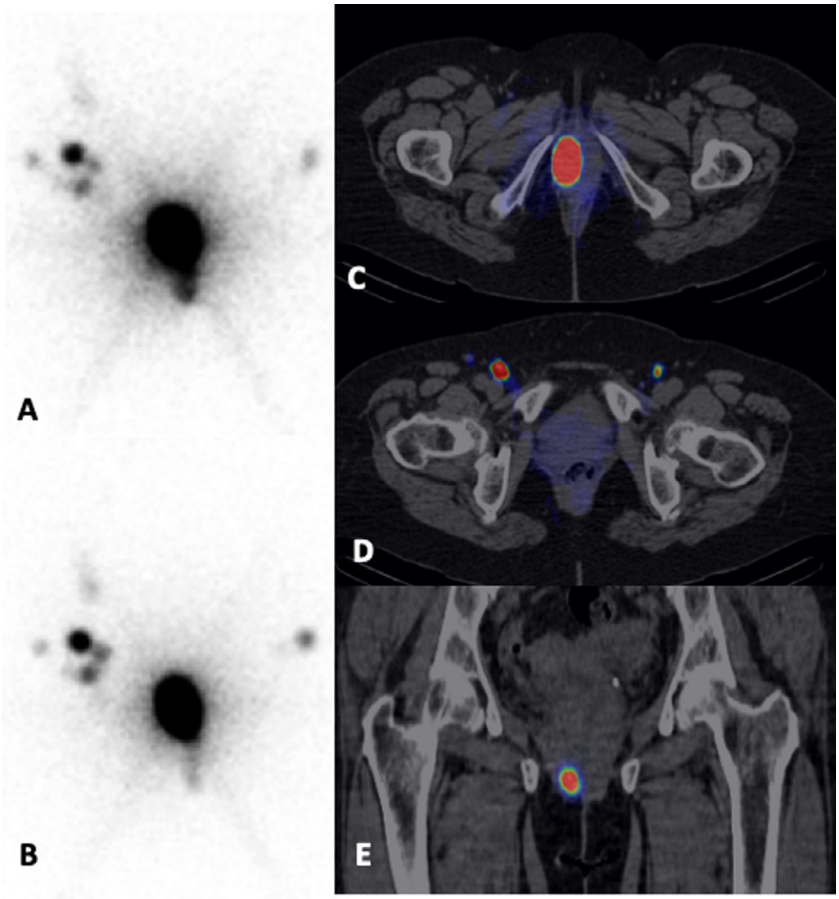

Figure 5 A 67-year-old patient with right sided vaginal melanoma. underwent sentinel lymph node scintigraphy. After two injections of about 30 MBq each in the periphery of the scar, several focal uptakes were observed in planar acquisitions at 10 and 60 minutes (A and B). The fused SPECT/CT views showed the injection site (C and E) and bilateral lymph node uptake in the inguinal areas (D). All nodes showed no metastatic spread.

synergy with blue dyes in order to optimize detection rates. In a prospective multicenter study (SENTI-ENDO) using cervical dual injection of [^{99m}Tc]-labeled colloid and patent blue in 125 eligible patients with early-stage EC, Ballester et al showed an ODR of 89% with sensitivity of 84% and NPV of 97% when considering patient-based analysis.[125] How et al also showed in a 100 patients study using a pericervical combined injection (blue and [^{99m}Tc]-labeled colloid) adequate detection rates with ODR of 92% (bilateral detection rate of 72%), sensitivity of 89%, and NPV of 99%.[126] Obviously, as for other gynecologic tumors, SPECT/CT imaging improves ODR from 40%-67% to 84%-88% (comparing to planar lymphoscintigraphy), and bilateral detection increased from 39% to 53%[127,128] with good reproducibility,[129] providing a meaningful roadmap for the surgeon during intraoperative detection of SNs (especially for uncommon lymphatic drainage pathways).

Since few years, ICG is increasingly used, showing better detection performances than conventional tracers, especially in obese patients.[117,130-132] In a randomized controlled trial, Rozenholc et al showed that the use of ICG instead of blue dye results in a 26.5% (95% confidence interval 17.4%-35.6%) increase of SLN detection rates per hemipelvis in women with endometrial cancer.[133] In a study of 100 patients using an injection of a mixture of blue dye [^{99m}Tc]-labeled colloids and ICG, How et al showed similar SLN detection rates between ICG and [^{99m}Tc]-labeled colloids with a ODR of 87% vs 88% (P= 0.83) and a bilateral DR of 65% vs 71% (P= 0.36), respectively.[134] Recently, Togami et al showed good detection rates in a prospective study of 113 patients using a combination of [^{99m}Tc]-labeled colloids (with preoperative SPECT/CT) and ICG.[135] In this study, the detection rates for ICG for pelvic SLN, bilateral pelvic SLN, and para-aortic SLN were 96%, 80%, and 55%, respectively, with sensitivity of 91% and NPV of 99%.

To conclude, LN assessment is still controversial for early-stage endometrial cancer despite several studies and a last paper with a cohort of 5546 patients published in 2019, showed that routine systematic lymphadenectomy does not improve disease-free or overall survival compared to SLN biopsy (for all histopathologic grades, including high-risk grade) and is responsible of more frequent comorbidities.[136] In this context, several studies showed that SLN is a feasible procedure with accurate detection rates especially when a pericervical injection of combined [^{99m}Tc]-labeled colloids (with preoperative SPECT/CT) and ICG is performed.

Vaginal Cancer

Vaginal cancers represent 1%-2% of all gynecologic malignancies. The majority of invasive vaginal cancers are squamous cell carcinomas and the second most common type is melanoma (less of 4% of vaginal tumors).[137] The SLN procedures are useful not only in staging of tumor but also in establishing appropriate therapy,[138] suggesting an early LN dissection in case of positive SLN[139] and, on the other side, reducing the number of patients undergoing unnecessary extensive lymphadenectomy in absence of metastatic disease.[140] However, since the number of published studies about SLN procedures in vaginal cancers is fairly scarce, the role of SLN biopsy and LN dissection is still unclear, consequently that the staging used by FIGO remains clinical. The commonest method of SLN mapping starts with a preoperative peritumoral injection of radioactive [^{99m}Tc] colloid and preoperative lymphoscintigraphy, then followed by intraoperative injection of a blue dye and detection of the SLN by gamma probe[141]; it was shown that in patients undergoing surgical cancer resection, 82% of SLNs were detected by both [^{99m}Tc]-labeled colloid and blue dye, 9% only by the gamma probe, and 9% were only blue dye positive.[142] In the first prospective clinical study of pretreatment lymphatic mapping and SLN detection published by Frumovitz et al on 14 patients affected by vaginal cancer, (7 squamous cell carcinomas, 5 vaginal melanomas, 1 adenocarcinoma, and 1 undifferentiated carcinoma), at least 1 SLN was identified by presurgical lymphoscintigraphy in 79% of patients.[142] This was in agreement to the study of Vam Dam et al in which there was a complete concordance between the status of the SLN and the histologic findings at lymphadenectomy.[143] Moreover, bilateral SLN were found in 55% of patients in whom SLN were identified; the bilateralism was seen in 100% of patients with midline lesions and only in 38% of those with lateral lesions. These data showed that lymphatic drainage from the primary tumor does not always follow the lymphatic channels that would have been predicted anatomically. In fact, several papers have shown that tumors arising from the proximal third of the vagina metastasize in paracolpic lymph vessels to pelvic LNs, those arising from the middle third of the vagina in inguinal and pelvic LNs, whereas tumor sites in the distal third of vagina lead only to inguinal LN metastases.[139,144-148]

Image acquisition has also been subject of few studies,[144,149] given that planar images present some limitations.[150] SPECT/CT imaging is able to achieve the precise anatomic localization of SLN on cross-sectional imaging (Fig. 6), increasing the sensitivity of SLN detection and allowing to reduce false positive interpretations (due to a stasis of radiotracer in lymphatic vessels, a possible contamination or masked nodes by the high activity of the injection site). FNR of this technique was 0% and a NPV of 100%.[144] The reasons for the absence of uptake of [^{99m}Tc] colloid in SLN may be due to fibrosis secondary to previous multiple local excisions or lymphatic channel blockage related to transit metastases.[146] In conclusion, although SLN detection is not a standard of care to date, efforts are ongoing in order to reduce the surgical morbidity without impacting its efficacy in patients affected by vaginal cancers.

Ovarian Cancer

Ovarian cancer represents the second most common gynecologic malignancy, with a prevalence of 30-50 per 100,000 women, and it is the cause of more than half of all deaths related to gynecologic cancer.[151] The incidence of positive LNs in early-stage ovarian cancer is low, ranging from 5% to 15%,[152] while in advanced-stage cancer LNs, dissemination is over 20%,[153] and very often para-aortic SLN are found

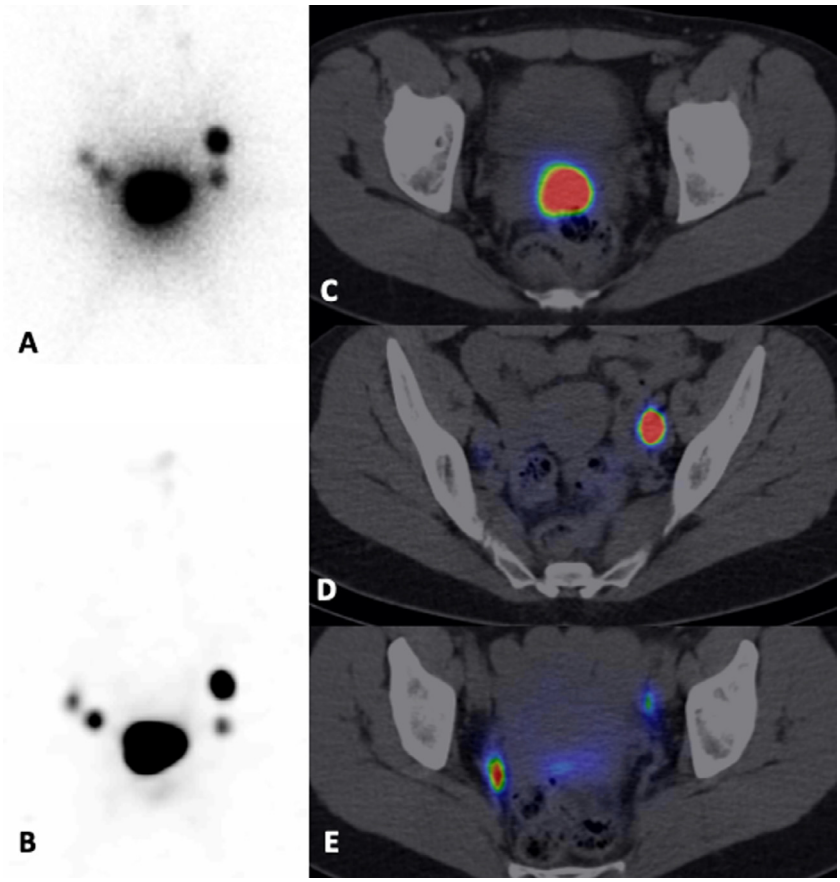

Figure 6 A 50-year-old woman with FIGO IB1 cervical adenocarcinoma underwent sentinel lymph node scintigraphy. After injection of about 120 MBq in four peritumoral points, planar images were acquired at 15 and 60 minutes (A and B). The fused SPECT/CT views showed the cervical injection site with no pelvis contamination (B), bilateral pelvic SNL drainage with a habitual iliac external left node uptake and a rarer right para-metrial node uptake (D and E).

below or above the inferior mesenteric artery.[154,155] On the other hand, in unilateral ovarian tumor cases, only ipsilateral LNs dissemination were positive in 54% of patients; contralaterality of the LN metastases was found in 13% of patients and bilateralism in 33% of them.[156]

Then, since the routine pelvic and/or aortocaval lymphadenectomy is associated with high rates of symptomatic postoperative lymphocele and lower-limb lymphedema,[157] in selected cases the occurrence of lymphatic complications could be achieved by using less invasive techniques, such as SLN detection and pathologic examination.

In fact, only few papers have explored the use of SLN detection during surgery of ovarian cancer. The most common method used to date is intraoperative injection of [^{99m}Tc]-labeled colloid and blue dye,[154] although some recent studies described an easier and faster procedure by using only the fluorescent tracer ICG.[158,159]

The injection site has also been debated; it seems that the best detection rate of SLN is achieved injecting tracers near the hilum of the ovary (94%-100%).[160] However, the injection into both ovarian ligaments shows a quite similar detection rate of SLN (90%-100%). In case of injection in the cortex, a lower detection rate is observed (40%-100%), with a higher risk of capsule rupture and tumor dissemination during surgery.[161]

Although the exact timing for the intraoperative detection of positive LNs remains undefined, it seems that 10-20 minutes is an optimal time interval between radiopharmaceutical injection and SLN detection,[154,162-164] with excellent SLN detection rate (100%, 94%, 96%); furthermore, it was showed that in case of injection of [^{99m}Tc phytate], a waiting time of 10 minutes is sufficient, with a detection rate of 84%.[164] All SLN detection failure in these studies occurred in patients with: ovarian torsion which can disrupt the lymphatic flow of the ovaries,[164] dermoid cyst with a high number of adhesions preventing access to the ovarian ligaments,[154] or in case of obstruction lymph flow by LN metastases.[162]

In conclusion, experience on SLN mapping in ovarian tumors is very limited and SLN detection is not yet standard of care. In fact, the accuracy of the SLN concept in ovarian cancer and its clinical applications should be evaluated in larger multicentric studies.

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