Clinical and Translational Imaging
https://doi.org/10.1007/s40336-024-00619-2

REVIEW

Sentinel node biopsy in gynaecological cancers: state of art and future perspectives

Valentina Fuoco[1] · Serena Sassano[2] · Simona M. Fragomeni[3] · Nicolò Bizzarri[3] · Damiano Arciuolo[4] · Isabella Bruno[1] · Daniela Di Giuda[2,5] · Angela Collarino[5]

Received: 31 October 2023 / Accepted: 10 January 2024

Abstract

Purpose This review aims to provide an overview of current knowledge and future perspectives on sentinel node biopsy in gynaecological cancers.

Methods Literature research in the PubMed/MEDLINE database was carried out to identify relevant studies on sentinel node biopsy in gynaecological cancers. We selected only original studies, published in the English language and including a minimum of nine patients.

Results The most relevant results on sentinel node biopsy in gynaecological cancers were summed up, focusing on clinical indications, technical aspects, preoperative and intraoperative procedures and the latest technological advances.

Conclusion Sentinel node biopsy has been widely validated in well-selected patients with early-stage vulvar, cervical and endometrial cancers. It is essential to standardise the acquisition protocol, including SPECT/CT imaging, for an improved surgical planning and a personalised approach. Recent technological advances, such as hybrid tracers and intraoperative tools, may efficiently guide gynaecological cancer surgery.

Keywords Gynaecological cancers · Sentinel node biopsy · SPECT/CT · Hybrid tracer

Introduction

Nowadays, there is growing interest in the application of minimal invasive techniques for the surgical treatment of early-stage gynecological cancers. Sentinel node biopsy (SNB) provides accurate lymph node staging, reducing the high risk of complications compared to full lymphadenectomy [1]. It enables the identification of unusual lymphatic drainage patterns [2] and increases the detection of micrometastases (>0.2 but ≤2 mm) and isolated tumour cells (ITCs, ≤0.2 mm) by immunohistochemistry [3]. More recent advances in intraoperative tools (e.g., portable gamma camera and robotic-guided procedure) and new hybrid tracers, such as indocyanine green (ICG)-^{99m}Tc-nanocolloid, are useful in guiding surgery. However, SNB should be performed in experienced centres [1].

This narrative review aims to provide an overview of current knowledge and future perspectives on SNB in gynaecological cancers, including vulvar cancer, cervical cancer and endometrial cancer.

Methods

A literature search in the PubMed/MEDLINE database was performed to identify relevant studies evaluating SNB in gynaecological cancers. The research strategy was based on the combination of the keywords “gynaecological cancers”,

✉ Daniela Di Giuda
daniela.digiuda@unicatt.it

1 Nuclear Medicine Unit, Ente Ecclesiastico Ospedale Generale Regionale “F.Miulli”, Acquaviva delle Fonti, Bari, Italy

2 Institute of Nuclear Medicine, Università Cattolica del Sacro Cuore, Rome, Italy

3 Gynecologic Oncology Unit, Department of Women, Children and Public Health Sciences, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

4 Unit of Gynecopathology, Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

5 Nuclear Medicine Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy

Published online: 04 March 2024

"SNB", "lymphoscintigraphy", "SPECT/CT", "hybrid tracer" and their synonyms. We selected only original studies on SNB in gynaecological cancers, published in the English language and including a minimum of nine patients. Review articles, letters to the editor, editorials and case reports were ruled out. The search was last updated on 21 April 2023 and had no date limit. Two reviewers independently assessed the title, abstract and full text of the articles to confirm their eligibility. A cross-check of the references of all included articles was performed to identify additional studies.

Results

As a result of the literature search and selection, a total of 33 studies were included [2–34]. Most studies involved patients undergoing preoperative and intraoperative sentinel lymph node (SLN) mapping [2–4, 6–9, 11–14, 17–22, 24, 25, 27, 29, 31–34]. Furthermore, most studies detected SLN by combining radiotracer and dye agent [2–9, 11–14, 17–25, 27, 29, 31, 33, 34]. Only five studies reported on the role of hybrid tracer [17, 22, 25, 29, 32]. Four studies investigated the clinical outcome in SLN-negative patients [5, 20, 23, 30], whereas eight studies examined the role of ultrastaging analysis of SLNs [2, 9, 10, 15, 16, 18, 26, 28].

Discussion

Vulvar cancer

Clinical indications for SNB

Vulvar cancer is a rare disease, with an incidence rate of 2.5 per 100.000 women per year [35] and squamous cell carcinoma accounts for about 90% [36]. The most important prognostic factor is the presence of lymph node metastases [37]. This malignancy typically spreads to the inguinal basin, whereas clitoris and perineum cancers may directly spread to the pelvic region [38]. As only 25% to 35% of patients with early-stage vulvar cancer have groin metastases [37], inguinofemoral lymphadenectomy (IFL) represents overtreatment in most of these patients and is associated with a high risk of postoperative short- and long-term morbidity [39]. The GOG-173 trial (Gynecologic Oncology Group-173) demonstrated that SNB is a safe and alternative technique to IFL in patients with squamous cell cancer of the vulva smaller than 4 cm, with a false-negative predictive value of 2.0% [12]. Moreover, the GROINSS-V trial (GRoningen INternational Study on Sentinel nodes in Vulvar cancer) showed that the negative SLN was associated with a low groin recurrence rate (2.3% after a median follow-up of 35 months), less postoperative morbidity and good survival [5]. Similar results were obtained by Te Grootenhuis et al. also with a long follow-up [23]. On the basis of GROINSS-V and GOG-173 trials, SNB is currently considered the standard treatment for well-selected women with clinically/radiologically negative lymph nodes (cN0) [1, 40, 41] (Table 1). Lateral tumours (more than 1–2 cm from midline structures) mainly spread to the ipsilateral lymph nodes, and are therefore scheduled for ipsilateral SNB [41, 42]. Conversely, midline tumours (until 2 cm from midline structures) may drain to both groins [38], thus bilateral SNB is mandatory [41]. Recently, the reliability of SNB (none false negative) has been demonstrated even in cN0 patients who are ruled out from this procedure due to: (a) T > 4 cm or multifocal tumour, (b) complete tumour diagnostic excision, (c) contralateral nodal involvement and (d) local recurrence [24].

Preoperative mapping

Technetium (^{99m}Tc)-radiolabelled colloids are lymphatic radiotracers typically employed for SLN mapping. In Europe, the most common colloid is nanocolloidal albumin [1] (Table 2).

^{99m}Tc-nanocolloid is injected intradermally into four quadrants around the edge of the tumour [1, 40]. Typically, 4 aliquots of 37 MBq in 0.1 mL of radiotracer are used in the 1 day protocol, whereas 4 aliquots of 74 MBq in 0.1 mL in the 2 day protocol [1, 40]. Immediately after the injection, pelvic dynamic images of 15–30 min are acquired in anterior and posterior projections. Therefore, anterior and lateral static images of 3–5 min are obtained 20–30 min (early images) and 60–120 minutes (late images) post injection [1, 40]. Dynamic and early static images provide lymphatic

Table 1 Indications for SNB in gynaecological cancers [1, 41, 48, 61]

Type of cancer	Indications
Vulvar cancer	FIGO 2021 stage IB/II: - unifocal primary tumour - T≤4 cm - >1 mm depth of stromal invasion - cN0
Cervical cancer	FIGO 2018 stage IA2/IB1/IB2/IIA1: - T<4 cm - >3 mm depth of stromal invasion - cN0
Endometrial cancer	FIGO 2009 stage I/II: - uterine-confined disease - cN0

SNB sentinel node biopsy; *FIGO* International Federation of Gynecology and Obstetrics; *cN0* clinically negative node(s)

Table 2 Advantages and disadvantages of lymphatic tracers for SNB

Tracer	Advantages	Disadvantages
^{99m}Tc-nanocolloid	Preoperative lymphatic mapping	a) Ionizing radiation exposure b) Preoperative injection
Blue dye	a) Intraoperative injection, after anesthesia b) Direct visualisation of lymphatic channels and SLNs c) Lack of ionizing radiation d) Availability and easy to handle	a) Very low penetration into tissue b) Staining of the surgical field c) Contraindications: pregnancy; lactation; anaphylactic allergic reactions
ICG	a) Intraoperative injection, after anesthesia b) Real-time intraoperative visual guidance c) No staining of the surgical field d) Lack of ionizing radiation e) Availability and easy to handle	a) Low tissue penetration depth b) Necessity of intraoperative fluorescence camera system c) Rapid diffusion through lymphatic pathway
ICG-^{99m}Tc-nanocolloid	Preoperative lymphatic mapping and intraoperative real-time fluorescent guidance	a) Ionizing radiation exposure b) Preoperative injection c) Necessity of intraoperative fluorescence camera system

SNB sentinel node biopsy; *SLNs* sentinel lymph nodes; *ICG* indocyanine green

routes and first-draining SLN visualisation whereas late images are useful in differentiating SLNs from higher-echelon nodes [40] (Fig 1). Furthermore, planar lymphoscintigraphy permits the detection of unexpected drainage patterns prior to surgery [14]. After the delayed planar acquisition, a reference source, such as ^{57}Co-penmarker, is employed to localise SLNs on the overlying groin skin. Then, SLN site is marked with indelible ink in the anterior and lateral projections, allowing for a more selective incision. Finally, SPECT/CT images are obtained [1]. Due to the better contrast and spatial resolution of tomographic acquisition, as compared to planar lymphoscintigraphy, SPECT/CT usually identifies additional SLNs and higher echelon nodes [19]. This allows their accurate anatomical localisation, as well as unusual lymphatic drainage pathway identification [4, 19, 21]. As a result, SPECT/CT may personalise lymphatic

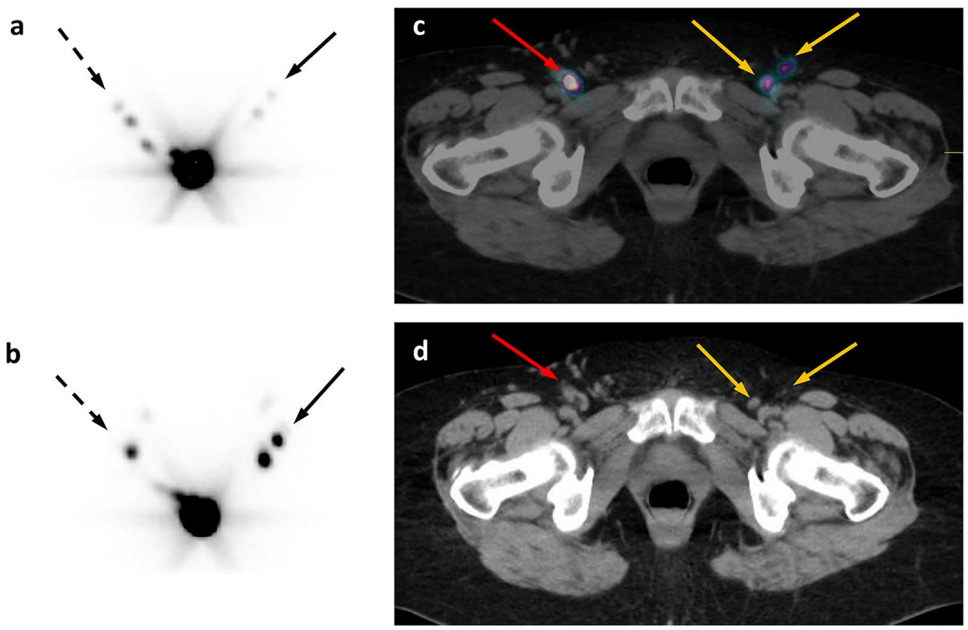

Fig. 1 A 59 year-old woman who had a median vulvar tumour. The early anterior planar image (**a**) showed bilateral lymphatic drainage with the visualisation of two focal radiotracer uptakes (arrow) in the left groin and three focal uptakes (dashed arrow) in the right groin. The late anterior planar image (**b**) showed two SLNs (arrows) in the left groin and only one SLN (dashed arrow) in the right one. The other findings observed in the early image were no longer visible as they represented transient radioactivity accumulation in enlarged lymphatic vessels. Transaxial-fused SPECT/CT image (**c**) confirms the presence of two focal uptakes (yellow arrows) in the left groin, corresponding to two lymph nodes (yellow arrows) on transaxial low-dose CT (**d**), and a single focal uptake (red arrow) in the right groin, corresponding to one node (red arrow) on low-dose CT (**d**)

mapping for better surgical planning. In this context, Collarino et al. showed that lymphatic drainage of vulvar cancer predominantly occurs in the medial regions of the groin [19].

Intraoperative procedures

Blue dye was the first optical tracer for intraoperative lymphatic mapping in vulvar cancer [43] (Table 2). In the last years**,** ICG has become the most widely used optical tracer for intraoperative SLN mapping in vulvar cancer [44] (Table 2). Meads et al. showed that the combined use of blue dye and radiotracer improved intraoperative detection (97.7%) [45]. More recently, Rundle et al. reported that the combined use of ICG and ^{99m}Tc-nanocolloid resulted in a higher intraoperative detection rate than that obtained by blue dye and ^{99m}Tc-nanocolloid (84% vs. 69%, respectively) [34]. In vulvar cancer, prior to groin surgery, blue dye or ICG should be injected around the tumour in the same site as radiotracer injections [1]. The hand-held gamma probe is placed on the groin skin to identify the area of highest radioactivity, thus guiding the incision [1, 40]. The probe is then used intraoperatively to localise SLNs and remove them and, after SLN excision, it is employed to measure SLN radioactivity *ex vivo* [1]. However, when injecting ICG, a fluorescence probe is required for intraoperative localisation. All removed SLNs are referred for pathological examination. They routinely undergo haematoxylin and eosin (H&E) staining and, if no metastases are detected, ultrastaging with cytokeratin 1% AE1:AE3 antikeratin solution is performed to reveal low-volume metastases as micrometastases (tumour deposits between 0.2 and 2.0 mm) and/or ITCs (tumour deposits not exceeding 0.2 mm or single non-cohesive cytokeratin-positive tumour cells). Currently, no SLN metastasis cut-off size has been found below which the risk of additional inguinal metastases may be negligible. Therefore, additional inguinal treatment must be performed for all patients with metastatic SLNs [3].

Cervical cancer

Clinical indications for SNB

Cervical cancer is the fourth most common malignancy in women worldwide [46], with an incidence rate of 7.7 per 100.00 women per year [47] and squamous cell carcinoma is the most frequent histotype (80% of all cervical cancers) [48]. The main prognostic factor is locoregional nodal invasion. Indeed, this malignancy typically spreads to the obturator nodes, followed by the external iliac, the common iliac and, lastly, the para-aortic nodes [49]. In early-stage cervical cancer, the incidence of metastatic pelvic nodes ranges from 11.5 % to 21 % [50], therefore pelvic lymph node dissection (PLND) is regarded as overtreatment in most of these patients and is associated with a high risk of postoperative complications (e.g., vessel and nerve injury, ureteral wound, infection, lymphocele, lymphedema) [51].

The SENTICOL (Ganglion Sentinelle dans le Cancer du Col) longitudinal study showed that SNB is a safe and alternative technique to PLND in patients with early cervical cancer, with a bilateral SLN detection rate of 76.5% and an NPV of 98.2% [9]. Furthermore, the SENTICOL trial demonstrated the usefulness of SNB mapping to discover unusual lymph drainage patterns and to provide enhanced detection of micrometastases by pathological ultrastaging [2]. In addition, SNB and pathological ultrastaging are more cost-effective than PLND [52]. The SENTICOL-2 study compared the SNB group with the SNB group followed by PLND, showing significantly lower surgical morbidity in the SNB group. The 3 year recurrence-free survival was similar between the two groups [30]. In light of these results [2, 9, 30], SNB is indicated in well-selected cN0 early-stage patients (Table 1). Being the cervix a central pelvic organ, bilateral pelvic lymph node staging is required [28, 48]. In case of mapping failure on a hemipelvis, side-specific lymphadenectomy should be performed to avoid possible false negatives [48].

Preoperative mapping

In cervical cancer, the radiotracer is commonly injected into the cervix, usually in 2 or 4 points avoiding the necrotic part of the tumour [1, 48]. Typically, four aliquots of 110 MBq in a total volume of 2 mL (0.5 mL per depot) are employed in the 1 day protocol, whereas four aliquots of 220 MBq in a total volume of 2 mL (0.5 mL per depot) in the 2 day protocol [1].

For cervical cancer, pelvic dynamic images are not acquired. Early planar images are obtained in anterior and lateral views after radiotracer injection, whereas delayed planar images are acquired after 120 min [1]. While the former static acquisition enables to visualise lymphatic ducts and the first draining lymph nodes, the latter allows to identify additional SLNs as well as to differentiate them from higher-level lymph nodes [53, 54]. In addition, SPECT/CT imaging is required for preoperative SLN mapping due to the deep lymphatic drainage of these tumours [1]. Indeed, the technique provides an accurate anatomical location of the SLNs and detects a greater SLN number than planar images [13, 55]. Moreover, it is possible to identify SLNs close to the injection site (i.e., parametrial SLNs in cervical cancer), as well as aberrant lymphatic drainage pathways (i.e., paravaginal, paravesical, gluteal and retrovesical SLNs) [7]. Ultimately, SPECT/CT is a helpful tool to visualise bilateral drainage and reduce false positive results (due to external contamination or radioactivity in enlarged

lymphatic vessels), thus enabling proper surgical planning and shorter surgery time [11, 54].

Intraoperative procedures

In cervical cancer, the optical tracer (blue dye or ICG) is commonly injected into the cervix before surgery, in the same sites as radiotracer injections. The randomized phase III FILM trial demonstrated that ICG tracer identified more bilateral SLNs than blue dye [56]. The gamma probe is used intraoperatively to localise the SLNs [1]. Shortly after excision, the probe is employed to measure SLNs radioactivity *ex vivo* [1]. Intraoperative localisation of fluorescent lymph nodes requires a fluorescence probe upon ICG injection. In the last decade, suitable gamma probes have been developed for laparoscopic surgery. However, it is worth taking into account possible interferences during laparoscopic probe scanning: a) proximity to the injection site; b) uterus enlargement in endometrial cancer patients; c) increased radioactivity in the ureters due to physiologic kidney excretion; d) liver activity as a result of radiocolloid uptake in the reticuloendothelial system. Therefore, in this context, intraoperative visual guidance (i.e., blue dye or ICG) is particularly useful [57]. Moreover, the intraoperative gamma probe may be supplemented with a portable gamma camera or an intraoperative freehand SPECT prior to SLN resection. Indeed, advantages of a portable gamma camera include increased sensitivity in localising parametrial SLNs, better discrimination of liver activity interference for para-aortic SLNs localisation, and improved ability to establish complete SLN excision [6]. On the other hand, freehand SPECT yields virtually real-time information on SLNs depth, and preoperative imaging data can be included to provide anatomical landmarks and intraoperative navigation [58]. All excised SLNs are referred for pathological examination with H&E staining. As with vulvar cancer, when this first histological evaluation does not reveal metastases, ultrastaging (including serial H&E sectioning and immunohistochemistry staining with pancytokeratin antibodies), is performed to detect low-volume metastases [48]. Cibula et al. demonstrated that the presence of SLNs micrometastases was associated with significantly reduced overall survival in 645 patients with early-stage cervical cancer [10].

Endometrial cancer

Clinical indications for SNB

Endometrial cancer is the most common gynaecological tumour with an incidence rate of 27.6 per 100.000 women per year [59]. It usually occurs in older age (≥55 years) and endometrioid adenocarcinoma is the most frequent histotype [60]. Locoregional nodal involvement is associated with a worse prognosis [61]. As the malignancy mainly spreads to the pelvic and para-aortic nodes, a full lymphadenectomy has been recommended for all patients to provide accurate lymph node staging for guiding adjuvant therapy, if necessary [61]. Two randomized controlled trials demonstrated that complete pelvic and para-aortic lymphadenectomy (LAD) has a high risk of postoperative complications, with no benefits in terms of overall and recurrence-free survival in clinically early-stage disease [62, 63]. The SENTI-ENDO trial showed that SNB is a possible alternative to LAD in 125 patients with low- and intermediate-risk endometrial cancers [8]. Similar findings were also reported in the FIRES trial [64]. Long-term results of the SENTI-ENDO trial revealed a recurrence-free survival of 84.7%, thereby supporting the impact of SNB on surgical management and adjuvant therapy indications [20]. Accordingly, SNB may be a suitable alternative to LAD in well-selected patients with apparent uterine-confined disease, thus avoiding overtreatment and reducing postoperative morbidity [61]. (Table 1). In addition, Soliman et al. suggested that SNB could be an alternative technique to LAD in patients with high-risk endometrial cancer (e.g., grade 3, serous, clear cell, carcinosarcoma), showing a SLN detection rate of 89% [65].

Preoperative mapping

The radiotracer is commonly injected into the cervix, usually in 4 points [1] and can be performed the day prior to surgery, thus enabling a preoperative lymphatic mapping. Typically, the total administered activity may range from 40 to 185 MBq and the volume injected from 0.5 to 8 mL [1]. Acquisition protocol, including planar lymphoscintigraphy and SPECT/CT, is the same as for cervical cancer. Given the deep lymphatic drainage of the corpus uteri, preoperative SPECT/CT plays an important role in providing tissue attenuation correction with an improved anatomical localization of SLNs and detection of additional SLNs in other basins [7, 13, 31].

Intraoperative procedures

For endometrial cancer, the optical tracer (blue dye or ICG) is commonly injected into the cervix before surgery in 2 points (at 3 and 9h) [61]. The FILM trial confirmed that ICG is able to identify more SLNs than blue dye for uterine cancers [56]. More recently, Cabrera et al. reported that the combination of radiotracer and ICG appears to be superior to radiotracer-blue dye in terms of bilateral detection rates [27]. The surgical procedure and pathological analysis are the same as previously described for cervical cancer. SLN mapping with pathologic ultrastaging may increase the detection of nodal metastases with low false-negative rates, avoid unnecessary surgical complications in patients with

negative SLNs and may have an impact on prognosis [15, 16]. In particular, Raimond et al. showed that SNB with ultrastaging detected metastatic SLNs 3-fold more often than LAD, thereby improving staging with an impact on adjuvant therapy [18]. Plante et al. showed that patients with SLN ITCs had a better progression-free survival than those with SLN macrometastases; no difference in overall survival were found between patients with negative SLNs, ITCs and micrometastases, suggesting that the presence of ITCs have a little benefit from adjuvant treatment [26].

Future perspectives

Nowadays, there has been growing interest in the use of ICG-^{99m}Tc-nanocolloid, a hybrid tracer combining a radioactive and fluorescent guide after a single injection to optimize the SLN procedure (Table 2).

Mathéron et al. evaluated the feasibility of this multimodal surgical guidance for SNB in 15 patients with vulvar cancer. They observed that 98% of the SLNs were radioactive on excision, 96% were fluorescent and only 65% were blue. The additional value of ICG was the better intraoperative visualisation of SLN with fluorescent imaging compared to blue dye [17]. Verbeek et al. assessed the performance of ICG-^{99m}Tc-nanocolloid in 12 women who underwent SNB for stage I vulvar cancer. They found an intraoperative SLN detection rate of 100%, thus confirming the added value of this dual-modality tracer [22]. More recently, Deken et al. have published the results of the first randomized controlled trial on SLN detection by hybrid tracer compared to ^{99m}Tc-nanocolloid and blue dye in 48 vulvar cancer patients. They demonstrated that intraoperative visualisation of SLNs with hybrid tracer was greater than the standard procedure, as fluorescent resected SLNs were significantly higher than blue SLNs (92.5% and 65.3%, respectively). Accordingly, fluorescence imaging has the potential to facilitate the procedure by direct visualisation of SLNs [29]. However, due to the limited penetration depth of near-infrared fluorescence imaging (approximately 5 mm into fatty tissue), SLN detectability in overweight patients may be challenging. Therefore, radioactive guidance is still required for the presurgical planning and identification of deeper lymph nodes [66]. In conclusion, ICG-^{99m}Tc-nanocolloid seems to be a promising radiotracer for preoperative and intraoperative SLN identification in vulvar cancer.

Recently, ICG-^{99m}Tc-nanocolloid has also been evaluated in cervical and endometrial cancers, providing promising results in terms of intraoperative SLN detection rate. Indeed, the hybrid tracer, which combines the benefits of radio- and fluorescence-guided surgery, may increase SLN detection rates. This is relevant in uterine tumours due to the presence of a complex network of pelvic lymphatic vessels. In their prospective study based on a cohort of 16 early cervical cancer patients, Paredes et al. first demonstrated the feasibility and safety of this hybrid tracer. They reported that the hybrid tracer identified bilateral SLNs in all patients with a higher detection rate than blue dye. Specifically, among the 69 SLNs defined during surgery, 66 (95.6%) were identified by their radioactivity signal, 67 (97.1%) based on their fluorescent signal whereas only 35 (50.7%) through their blue coloration. Moreover, no acute or early complications were detected during surgery nor in the immediate postoperative period, thereby demonstrating the safety of this procedure [25]. More recently, in their 52 intermediate- and high-risk endometrial cancer patients, Sanchez-Izquierdo et al. showed the feasibility and suitability of SNB with ICG-^{99m}Tc-nanocolloid administered by transvaginal ultrasound-guided myometrial injection (TUMIR approach). According to their results, this procedure may lead to an increase of SLN detection rate (up to 20% of patients in the series) and achieve an elevated para-aortic detection rate [32]. Based on these preliminary promising findings, hybrid tracer could become a valid alternative to the current combined technique (radiotracer and blue dye) for SNB in uterine cancers.

On the other hand, the real-time fusion of three-dimensional (3D) SPECT/CT and ultrasound represents a novel approach for preoperative SLN mapping that has been recently evaluated in vulvar cancer. Indeed, Garganese et al. demonstrated the feasibility of this co-registration and fusion of images in five women with vulvar cancer, leading to a successful procedure in all cases with a median overall time of 32 min (range: 25–40 min) [67].

Minimally invasive radio-guided technique has been recently implemented with the introduction of DROP-IN gamma-probe for robot-assisted radio-guided surgery. This innovative laparoscopic probe consists of a gamma window, connected to a control unit by a flexible wire, and is equipped with a grip feature which enables manipulation by the robotic laparoscopic grasper. The control unit is connected to the robotic system with a digital visual interface cable to integrate the numerical signal from the DROP-IN gamma-probe (counts per second) on the display of the robotic consol [33]. The first-in-human clinical study evaluating this new technology for radio-guided SLN detection was performed in prostate cancer patients. The authors demonstrated the ability of the DROP-IN gamma-probe to ease radio-guided SLN resection given its increased rotational freedom and manoeuvrability compared to the conventional rigid laparoscopic probe [68]. These results were confirmed by subsequent studies [33, 69, 70]. Indeed, Baeten et al. published the first-in-women pilot study on the feasibility and safety of the DROP-IN gamma-probe during robot-assisted SLN procedure in ten patients with early-stage cervical cancer. All the patients underwent preoperative ^{99m}Tc-nanocolloid cervical injection and SPECT/

CT imaging. Intraoperatively, the DROP-IN gamma-probe was used to guide SLN resection, achieving high overall and bilateral detection rates (100% and 80%, respectively) [33]. In line with previous studies on prostate cancer patients, Baeten et al. showed that DROP-IN technology improves manoeuvrability and surgical autonomous control of the probe during robot-assisted SLN detection compared to the conventional rigid laparoscopic gamma-probe [33]. However, these preliminary results must be confirmed by larger clinical trials, assessing the performance of robot-assisted SN procedure in gynaecological cancers.

Conclusions

SNB has been widely validated in well-selected patients with early-stage vulvar, cervical and endometrial cancers. There are controversies on the safe extension of SNB indication in high-risk endometrial cancer, although it should be investigated in larger clinical patient series to decrease surgical morbidity. Moreover, it is essential to standardise the acquisition protocol including SPECT/CT images that provide a valuable surgical roadmap and may lead to a decreased surgical time. Pathologic ultrastaging increases the detection of low-volume disease (micrometastases and ITCs) and future studies should confirm preliminary results regarding their impact on the prognosis and management of patients. In addition, the recent technological advances, such as hybrid tracers (e.g., ICG-^{99m}Tc-nanocolloid) and intraoperative equipment (portable gamma camera and SLN robotic-guided tools), may be a useful guide in gynaecological cancer surgery.

Author contributions VF, SS and AC wrote the main manuscript text. SS prepared figure 1. All authors reviewed the manuscript.

Funding Open access funding provided by Università Cattolica del Sacro Cuore within the CRUI-CARE Agreement.

Declarations

Conflict of interest The authors have no conflict of interest to disclose.

References

1. Giammarile F, Bozkurt MF (2014) The EANM clinical and technical guidelines for lymphoscintigraphy and sentinel node localization in gynaecological cancers. Eur J Nuc Med Mol Imaging 41(7):1463–1477. https://doi.org/10.1007/s00259-014-2732-8
2. Bats AS, Mathevet P, Buenerd A et al (2013) The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: Insights from the multicenter prospective SENTICOL study. Ann Surg Oncol 20(2):413–422. https://doi.org/10.1245/s10434-012-2597-7
3. Oonk MH, van Hemel BM, Hollema H et al (2010) Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: Results from GROINSS-V, a multicentre observational study. Lancet Oncol 11(7):646–652. https://doi.org/10.1016/S1470-2045(10)70104-2
4. Beneder C, Fuechsel FG, Krause T, Kuhn A, Mueller MD (2008) The role of 3D fusion imaging in sentinel lymphadenectomy for vulvar cancer. Gynecol Oncol 109(1):76–80. https://doi.org/10.1016/j.ygyno.2007.11.045
5. Van Der Zee AGJ, Oonk MH, De Hullu JA et al (2008) Sentinel node dissection is safe in the treatment of early-stage vulvar cancer. J Clin Oncol 26(6):884–889. https://doi.org/10.1200/JCO.2007.14.0566
6. Vidal-Sicart S, Doménech B, Luján B et al (2009) Sentinel node in gynaecological cancers. Our Exp. Rev Española Med Nucl (English Ed) 28(5):221–228. https://doi.org/10.1016/s1578-200x(09)70022-1
7. Pandit-Taskar N, Gemignani ML, Lyall A, Larson SM, Barakat RR, Abu Rustum NR (2010) Single photon emission computed tomography SPECT-CT improves sentinel node detection and localization in cervical and uterine malignancy. Gynecol Oncol 17(1):59–64. https://doi.org/10.1016/j.ygyno.2009.12.021
8. Ballester M, Dubernard G, Lécuru F et al (2011) Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 12(5):469–76. https://doi.org/10.1016/S1470-2045(11)70070-5
9. Lécuru F, Mathevet P, Querleu D et al (2011) Bilateral negative sentinel nodes accurately predict absence of lymph node metastasis in early cervical cancer: Results of the SENTICOL study. J Clin Oncol 29(13):1686–1691. https://doi.org/10.1200/JCO.2010.32.0432
10. Cibula D, Abu-Rustum NR, Dusek L et al (2012) Prognostic significance of low volume sentinel lymph node disease in early-stage cervical cancer. Gynecol Oncol 124(3):496–501. https://doi.org/10.1016/j.ygyno.2011.11.037
11. Kraft O, Havel M (2012) Detection of Sentinel Lymph Nodes in Gynecologic Tumours by Planar Scintigraphy and SPECT/CT. Mol Imaging Radionucl Ther 21(2):47–55. https://doi.org/10.4274/mirt.236
12. Levenback CF, Ali S, Coleman RL et al (2012) Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J Clin Oncol 30(31):3786–91. https://doi.org/10.1200/JCO.2011.41.2528
13. Belhocine TZ, Prefontaine M, Lanvin D et al (2013) Added-value of SPECT/CT to lymphatic mapping and sentinel lymphadenectomy in gynaecological cancers. Am J Nucl Med Mol Imaging 3(2):182–193
14. Coleman RL, Ali S, Levenback CF et al (2013) Is bilateral lymphadenectomy for midline squamous carcinoma of the vulva always necessary? An analysis from Gynecologic Oncology Group (GOG) 173. Gynecol Oncol 128(2):155–159. https://doi.org/10.1016/j.ygyno.2012.11.034

15. Kim CH, Khoury-Collado F et al (2013) Sentinel lymph node mapping with pathologic ultrastaging: a valuable tool for assessing nodal metastasis in low-grade endometrial cancer with superficial myoinvasion. Gynecol Oncol 131(3):714–9. https://doi.org/10.1016/j.ygyno.2013.09.027
16. Kim CH, Soslow RA, Park KJ, Barber EL et al (2013) Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer 23(5):964–70. https://doi.org/10.1097/IGC.0b013e3182954da8
17. Mathéron HM, Van Den Berg NS, Brouwer OR et al (2013) Multimodal surgical guidance towards the sentinel node in vulvar cancer. Gynecol Oncol 131(3):720–725. https://doi.org/10.1016/j.ygyno.2013.09.007
18. Raimond E, Ballester M, Hudry D et al (2014) Impact of sentinel lymph node biopsy on the therapeutic management of early-stage endometrial cancer: Results of a retrospective multicenter study. Gynecol Oncol 133(3):506–11. https://doi.org/10.1016/j.ygyno.2014.03.019
19. Collarino A, Donswijk ML, van Driel WJ, Stokkel MP, Valdés Olmos RA (2015) The use of SPECT/CT for anatomical mapping of lymphatic drainage in vulvar cancer: possible implications for the extent of inguinal lymph node dissection. Eur J Nucl Med Mol Imaging 42(13):2064–2071. https://doi.org/10.1007/s00259-015-3127-1
20. Daraï E, Dubernard G, Bats AS, Heitz D et al (2015) Sentinel node biopsy for the management of early stage endometrial cancer: long-term results of the SENTI-ENDO study. Gynecol Oncol 136(1):54–9. https://doi.org/10.1016/j.ygyno.2014.09.011
21. Klapdor R, Länger F, Gratz KF, Hillemanns P, Hertel H (2015) SPECT/CT for SLN dissection in vulvar cancer: Improved SLN detection and dissection by preoperative three-dimensional anatomical localisation. Gynecol Oncol 138(3):590–596. https://doi.org/10.1016/j.ygyno.2015.06.011
22. Verbeek FPR, Tummers QRJG, Rietbergen DDD et al (2015) Sentinel lymph node biopsy in vulvar cancer using combined radioactive and fluorescence guidance. Int J Gynecol Cancer 25(6):1086–1093. https://doi.org/10.1097/IGC.0000000000000419
23. Te Grootenhuis NC, van der Zee AGJ, van Doorn HC et al (2016) Sentinel Nodes in Vulvar Cancer: Long-Term Follow-up of the Groningen International Study on Sentinel Nodes in Vulvar Cancer (GROINSS-V) I. Obstet Gynecol Surv 71(3):157–159. https://doi.org/10.1016/j.ygyno.2015.09.077
24. Garganese G, Collarino A, Fragomeni SM, Rufini V (2017) Groin sentinel node biopsy and 18 F-FDG PET/CT-supported preoperative lymph node assessment in cN0 patients with vulvar cancer currently unfit for minimally invasive inguinal surgery: The GroSNaPET study. Eur J Surg Oncol 43(9):1776–1783. https://doi.org/10.1016/j.ejso.2017.06.018
25. Paredes P, Vidal-Sicart S, Campos F et al (2017) Role of ICG-^{99m}Tc-nanocolloid for sentinel lymph node detection in cervical cancer: a pilot study. Eur J Nucl Med Mol Imaging 44(11):1853–1861. https://doi.org/10.1007/s00259-017-3706-4
26. Plante M, Stanleigh J, Renaud MC, Sebastianelli A, Grondin K, Grégoire J (2017) Isolated tumor cells identified by sentinel lymph node mapping in endometrial cancer: Does adjuvant treatment matter? Gynecol Oncol 146(2):240–246. https://doi.org/10.1016/j.ygyno.2017.05.024
27. Cabrera S, Bebia V, Franco-Camps S, Forcada C et al (2020) Technetium-99m-indocyanine green versus technetium-99m-methylene blue for sentinel lymph node biopsy in early-stage endometrial cancer. Int J Gynecol Cancer 30(3):311–317. https://doi.org/10.1136/ijgc-2019-000923
28. Cibula D, Kocian R, Plaikner A et al (2020) Sentinel lymph node mapping and intraoperative assessment in a prospective, international, multicentre, observational trial of patients with cervical cancer: The SENTIX trial. Eur J Cancer 137:69–80. https://doi.org/10.1016/j.ejca.2020.06.034
29. Deken MM, van Doorn HC, Verver D et al (2020) Near-infrared fluorescence imaging compared to standard sentinel lymph node detection with blue dye in patients with vulvar cancer – a randomized controlled trial. Gynecol Oncol 159(3):672–680. https://doi.org/10.1016/j.ygyno.2020.09.044
30. Mathevet P, Lécuru F, Uzan C et al (2021) Sentinel lymph node biopsy and morbidity outcomes in early cervical cancer: Results of a multicentre randomised trial (SENTICOL-2). Eur J Cancer 148:307–315. https://doi.org/10.1016/j.ejca.2021.02.009
31. Navarro AS, Angeles MA, Migliorelli F et al (2021) Comparison of SPECT-CT with intraoperative mapping in cervical and uterine malignancies. Int J Gynecol Cancer 31(5):679–685. https://doi.org/10.1136/ijgc-2020-002198
32. Sánchez-Izquierdo N, Vidal-Sicart S, Campos F et al (2021) Detection of the sentinel lymph node with hybrid tracer (ICG-[99mTc]Tc-albumin nanocolloid) in intermediate- and high-risk endometrial cancer: a feasibility study. EJNMMI Res 11(1):124. https://doi.org/10.1186/s13550-021-00863-x
33. Baeten IGT, Hoogendam JP, Braat AJAT, Zweemer RP, Gerestein CG (2022) Feasibility of a drop-in γ-probe for radioguided sentinel lymph detection in early-stage cervical cancer. EJNMMI Res 12(1):36. https://doi.org/10.1186/s13550-022-00907-w
34. Rundle S, Korompelis P, Ralte A, Bewick D, Ratnavelu N (2023) A comparison of ICG-NIR with blue dye and technetium for the detection of sentinel lymph nodes in vulvar cancer. Eur J Surg Oncol 49(2):481–485. https://doi.org/10.1016/j.ejso.2022.09.015
35. Surveillance, Epidemiology and End Result Program (SEER), Cancer Stat Facts: Vulvar Cancer. https://seer.cancer.gov. Accessed 30 May 2023
36. Hacker NF, Eifel PJ, van der Velden J (2012) Cancer of the vulva. Int J Gynaecol Obs 119(2):90–96. https://doi.org/10.1016/S0020-7292(12)60021-6
37. Burger MP, Hollema H, Emanuels AG, Krans M, Pras EB (1995) The importance of the groin node status for the survival of T1 and T2 vulval carcinoma patients. Gynecol Oncol 57(3):327–334. https://doi.org/10.1006/gyno.1995.1151
38. Iversen T, Aas M (1983) Lymph drainage from the vulva. Gynecol Oncol 16(2):179–189. https://doi.org/10.1016/0090-8258(83)90092-6
39. Gaarenstroom KN, Kenter GG, Trimbos JB et al (2003) Postoperative complications after vulvectomy and inguinofemoral lymphadenectomy using separate groin incisions. Int J Gynecol Cancer 13(4):522–527. https://doi.org/10.1046/j.1525-1438.2003.13304.x
40. Collarino A, Fuoco V, Garganese G et al (2020) Lymphoscintigraphy and sentinel lymph node biopsy in vulvar carcinoma: update from a European expert panel. Eur J Nucl Med Mol Imaging 47(5):1261–1274. https://doi.org/10.1007/s00259-019-04650-8
41. Abu-Rustum NR, Yashar CM, Arend R et al (2024) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Vulvar cancer: Version 2.2024. http://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf. Accessed 30 October 2023
42. Oonk MHM, Planchamp F, Baldwin P et al (2017) European society of gynaecological oncology guidelines for the management of patients with Vulvar cancer. Int J Gynecol Cancer 27(4):832–837. https://doi.org/10.1097/IGC.0000000000000975
43. Levenback C, Burke TW, Gershenson DM et al (1994) Intraoperative lymphatic mapping for vulvar cancer. Obstet Gynecol 84(2):163–7
44. Koual M, Benoit L, Nguyen-Xuan HT, Bentivegna E, Azaïs H, Bats AS (2021) Diagnostic value of indocyanine green fluorescence guided sentinel lymph node biopsy in vulvar cancer: A systematic review. Gynecol Oncol 161(2):436–441. https://doi.org/10.1016/j.ygyno.2021.01.031

45. Meads C, Sutton AJ, Rosenthal AN et al (2014) Sentinel lymph node biopsy in vulval cancer: Systematic review and meta-analysis. Br J Cancer 110(12):2837–2846. https://doi.org/10.1038/bjc.2014.205
46. Arbyn M, Weiderpass E, Bruni L et al (2020) Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. Lancet Glob Heal 8(2):e191–e203. https://doi.org/10.1016/S2214-109X(19)30482-6
47. Surveillance, Epidemiology, and End Results Program (SEER), Cancer Stat Facts: Cervical Cancer. https://seer.cancer.gov. Accessed 30 May 2023
48. Abu-Rustum NR, Yashar CM, Arend R et al (2024) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Cervical cancer: Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed 30 October 2023
49. Benedetti-Panici P, Maneschi F, Scambia G et al (1996) Lymphatic spread of cervical cancer: An anatomical and pathological study based on 225 radical hysterectomies with systematic pelvic and aortic lymphadenectomy. Gynecol Oncol 62(1):19–24. https://doi.org/10.1006/gyno.1996.0184
50. Sakuragi N, Satoh C, Takeda N et al (1999) Incidence and distribution pattern of pelvic and paraaortic lymph node metastasis in patients with Stages IB, IIA, and IIB cervical carcinoma treated with radical hysterectomy. Cancer 85(7):1547–1554
51. Balaya V, Mathevet P, Magaud L et al (2019) Predictive factors of severe perioperative morbidity of radical hysterectomy with lymphadenectomy in early-stage cervical cancer: A French prospective multicentric cohort of 248 patients. Eur J Surg Oncol 45(4):650–658. https://doi.org/10.1016/j.ejso.2018.10.057
52. Brar H, Hogen L, Covens A (2017) Cost-effectiveness of sentinel node biopsy and pathological ultrastaging in patients with early-stage cervical cancer. Cancer 123(10):1751–1759. https://doi.org/10.1002/cncr.30509
53. Paredes P, Vidal-Sicart S (2012) Atlas of Lymphoscintigraphy and Sentinel Node Mapping. Springer, Milan, pp 249–268
54. Collarino A, Vidal-Sicart S, Perotti G, Valdés Olmos RA (2016) The sentinel node approach in gynaecological malignancies. Clin Transl Imaging 4(5):411–420. https://doi.org/10.1007/s40336-016-0187-6
55. Hoogendam JP, Veldhuis WB, Hobbelink MG et al (2015) 99mTc SPECT/CT Versus Planar Lymphoscintigraphy for Preoperative Sentinel Lymph Node Detection in Cervical Cancer: A Systematic Review and Metaanalysis. J Nucl Med 56(5):675–80. https://doi.org/10.2967/jnumed.114.152439
56. Frumovitz M, Plante M, Lee PS et al (2018) Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol 19(10):1394–1403. https://doi.org/10.1016/S1470-2045(18)30448-0
57. Collarino A, Feudo V, Vidal-Sicart S (2022) Sentinel node in gynecological cancers. In: Signore A (ed) Nuclear Medicine and Molecular Imaging. Elsevier, UK, pp 462–472
58. Vidal-Sicart S, Valdés Olmos R, Nieweg OE et al (2018) From interventionist imaging to intraoperative guidance: New perspectives by combining advanced tools and navigation with radioguided surgery. Rev Esp Med Nucl Imagen Mol 37(1):28–40. https://doi.org/10.1016/j.remn.2017.06.004
59. Surveillance, Epidemiology and End Result Program (SEER), Cancer Stat Facts: Uterine Cancer. https://seer.cancer.gov. Accessed 30 May 2023
60. Prat J (2004) Prognostic parameters of endometrial carcinoma. Hum Pathol 35(6):649–662. https://doi.org/10.1016/j.humpath.2004.02.007
61. Abu-Rustum NR, Yashar CM, Arend R et al (2024) NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Uterine Neoplasms: Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf. Accessed 30 October 2023
62. Kitchener H, Swart AMQQ et al (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet 373(9658):125–136. https://doi.org/10.1016/S0140-6736(08)61766-3
63. Panici PB, 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. https://doi.org/10.1093/jnci/djn397
64. Rossi EC, Kowalski LD, Scalici J et al (2017) A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol 18(3):384–392. https://doi.org/10.1016/S1470-2045(17)30068-2
65. Soliman PT, Westin SN, Dioun S et al (2017) A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. Gynecol Oncol 146(2):234–239. https://doi.org/10.1016/j.ygyno.2017.05.016
66. Brincat MR, Baron YM (2017) Sentinel lymph node biopsy in the management of vulvar carcinoma: An evidence-based insight. Int J Gynecol Cancer 27(8):1769–1773. https://doi.org/10.1097/IGC.0000000000001075
67. Garganese G, Bove S, Zagaria L et al (2019) Fusion of ultrasound and 3D single-photon-emission computed tomography/computed tomography to identify sentinel lymph nodes in vulvar cancer: feasibility study. Ultrasound Obstet Gynecol 54(4):545–551. https://doi.org/10.1002/uog.20364
68. Meershoek P, van Oosterom MN, Simon H et al (2019) Robot-assisted laparoscopic surgery using DROP-IN radioguidance: first-in-human translation. Eur J Nucl Med Mol Imaging 46(1):49–53. https://doi.org/10.1007/s00259-018-4095-z
69. Dell'Oglio P, Meershoek P, Maurer T et al (2021) A DROP-IN Gamma Probe for Robot-assisted Radioguided Surgery of Lymph Nodes During Radical Prostatectomy. Eur Urol 79(1):124–132. https://doi.org/10.1016/j.eururo.2020.10.031
70. Abascal Junquera JM, Mestre-Fusco A, Grootendorst MR, Vidal-Sicart S, Fumado L (2022) Sentinel Lymph Node Biopsy in Prostate Cancer Using the SENSEI® Drop-In Gamma Probe. Clin Nucl Med 47(1):86–87. https://doi.org/10.1097/RLU.0000000000003830