Clinical relevance of sentinel lymph node biopsy in early ovarian cancer

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The first-line treatment for early ovarian cancer typically involves primary debulking surgery aimed at maximal cytoreduction, alongside adjuvant chemotherapy if clinically indicated. Nodal assessment involving pelvic and para-aortic lymph node dissection is typically performed during the primary debulking surgery. However, the survival benefit of lymphadenectomy in patients with early ovarian cancer has not been well established, and the procedure is associated with longer operation time and higher perioperative complications. With the emergence of minimally invasive surgery as a potential alternative to laparotomy for early ovarian cancer, sentinel lymph node biopsy has been evaluated in this setting. In this review, we summarized the current literature regarding sentinel lymph node biopsy in patients with early ovarian cancer, focusing on the clinical relevance of this method, including its detection rate and diagnostic accuracy. Additionally, we discuss the current status of clinical trials investigating sentinel lymph node biopsy in early ovarian cancer cases.

Keywords: Ovarian cancer; Sentinel lymph node biopsy; Operative surgical procedure

Introduction

Ovarian cancer (OC) is the eighth most prevalent cancer in women worldwide, with a cumulative lifetime incidence risk of 0.73% [1]. Despite its relatively low incidence, OC has the most unfavorable prognosis among all gynecological malignancies, largely due to its asymptomatic and nonspecific nature. Approximately three-quarters of patients receive diagnoses at advanced stages, resulting in a mere 29.0% 5-year relative survival rate. Conversely, early stage OC demonstrates a significantly higher 5-year relative survival rate of 92.0%. The first-line treatment approach typically involves primary debulking surgery (PDS) for maximal cytoreduction, accompanied by adjuvant chemotherapy if clinically indicated [2]. Although PDS conventionally includes bilateral salpingo-oophorectomy, hysterectomy, omentectomy, and pelvic and para-aortic lymph node (LN) dissection (LND), the survival benefit of LND remains uncertain for presumed early stage OC. This uncertainty arises from the relatively low incidence of LN involvement (14.2%) [3]. Recent studies have suggested that LND in early stage OC does not correlate with improved progression-free or overall survival; however, it correlates with prolonged operation time and increased perioperative complications [4]. Nonetheless, excluding LN assessment during early OC evaluation could lead to an un-

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derestimation of LN metastasis, potentially resulting in the omission of necessary adjuvant chemotherapy. Minimally invasive surgery has emerged as an appealing alternative to laparotomy in early OC surgery due to reduced complication rates and non-inferior survival outcomes. Additionally, sentinel lymph node (SLN) biopsy has recently been evaluated in early OC [5,6].

The SLN is the 'first lymph node' where cancer cells are most likely to metastasize from the primary tumor. Since its introduction into the treatment of lower genitourinary tract cancer, SLN biopsy has evolved into the gold standard for melanoma and breast cancer. Although SLN biopsy is integrated into the treatment guidelines for vulvar, cervical, and endometrial cancers [7], studies on SLN biopsy in early OC remain limited due to the relatively small patient pool and the technical challenges of tracer injection in the ovary [8]. This review summarizes the current body of literature regarding SLN biopsy in patients with early ovarian cancer, emphasizing its clinical relevance, including detection rate and diagnostic precision. Furthermore, we discuss the current status of clinical trials investigating the utility of SLN biopsy in the context of early ovarian cancer.

Method

We searched the PubMed and EMBASE databases for studies and reports published between January 1995 and March 2023. A systematic search was performed using the following terms: 'ovarian cancer', 'ovarian tumor', 'ovary', 'sentinel', and 'sentinel lymph nodes'.

Studies were included if they were written in English and if the full text was available. Additionally, we reviewed the reference lists of the included studies and conducted a search for relevant studies that might have been omitted from our systematic search. Observational studies were also included. Furthermore, similar studies were conducted to exclude any overlapping studies from the study groups.

Results

This review included 10 studies involving 170 patients who underwent ovarian SLN mapping (Table 1). The patients were diagnosed with ovarian cancer or suspected malignant ovar-

ian masses, but three other studies included patients with endometrial or fallopian tube cancers. Five studies performed only open surgery (laparotomy), whereas the others used various surgical methods, such as laparoscopic and robotic surgery, for SLN mapping. Although LND protocols vary based on the study, comprehensive pelvic and para-aortic LND are usually performed after an SLN biopsy in malignant cases. However, only SLN tracing has been performed in benign or borderline cases in frozen section reports. Ultrastaging of the SLN was performed only in a study by Uccella et al. [9] (Table 2). In the following sections, we examine methodological considerations, including tracer type, injection site, and detection rate (defined as the rate of detection of at least one SLN per patient) for each approach.

1. Injection tracer

During SLN mapping, the tracer is injected into a site adjacent to the lymphatic drainage site of the tumor (just below the peritoneum), which enables the delineation of lymphatic pathways. Subsequently, intraoperative localization and excision of SLNs were performed. Various tracers have been used for early stage OC SLN mapping (Table 2). The main tracers used were blue dye, technetium-99m radiocolloid (Tc-99m), and indocyanine green (ICG). Negishi et al. [10] used activated charcoal solution as a tracer in their study. Each agent was administered alone or in combination.

2. Blue dye

When the concept of SLNs was proposed by Cabanas [11] in 1977 in patients with penile carcinoma, SLN localization was accomplished using contrast lymphangiography with (iodinated contrast agent). At that time, no radiolabeling or intraoperative localization imaging systems were available. Intraoperative blue dye lymphatic mapping was proposed by researchers from the MD Anderson Cancer Center to reduce the false-negative rate (25.0%) of the previously introduced SLN dissection [12]. However, determining the optimum timing between peritumoral injection and SLN localization is difficult for many surgeons because the dye drains rapidly, resulting in other nodes being mistaken for SLN. Moreover, the visual perception-dependent detection of blue-stained SLNs contributes to the technical difficulty of this method. Therefore, a radiocolloid tracer was introduced to the SLN localization method [13].

Table 1. General characteristics of SLN biopsy studies in patients with early ovarian cancer

Study	No. of patients	Tumor type/stage	Op method	LND protocol	Tracer	Ultrastaging
Negishi et al. (2004) [10]	11	Endometrial cancer (n=10), fallopian tube cancer (n=1)	LT		CH40 (activated charcoal solution)	-
Nyberg et al. (2011) [19]	16	Uterine cancer (normal ovaries)	LT		Tc-99m+blue dye	-
Kleppe et al. (2014) [14]	21	Ovarian mass (suspicious malignancy)	LT	Benign or borderline cases, SLN tracing only; Malignant cases, SLN followed by pelvic+paraaortic LND	Tc-99m+blue dye	-
Buda et al. (2017) [16]	10	Early ovarian cancer (n=7), cervical cancer (n=3)	LS	SLN followed by pelvic+paraaortic LND	ICG	-
Angelucci et al. (2016) [25]	5	Early ovarian cancer/I-II	LS	SLN followed by pelvic+paraaortic LND	ICG	-
Hassanzadeh et al. (2016) [15]	35	Ovarian mass (suspicious malignancy)	LT	Benign or borderline cases, SLN tracing only; Malignant cases, SLN followed by pelvic+paraaortic LND	Tc-99m±blue dye (used in 4 patients)	-
Lago et al. (2019) [34] Pilot study of SENTOV trial[a]	10	Ovarian cancer (confirmed by previous surgery or frozen section)	LT (n=7) LS (n=3)	SLN followed by pelvic+paraaortic LND	Tc-99m+ICG	-
Uccella et al. (2019) [9] Preliminary results of SELLY trial[b]	31	Early ovarian cancer/I-II	LT (n=1) LS (n=26) RB (n=4)	SLN followed by pelvic+paraaortic LND	ICG	+
Lago et al. (2020) [20] SENTOV trial phase II[c]	20	Ovarian cancer (confirmed by previous surgery or frozen section)	LT (n=11) LS (n=9)	SLN followed by pelvic+paraaortic LND	Tc-99m+ICG	-
Laven et al. (2021) [19] SONAR-2 trial phase I[d]	11	Ovarian cancer (confirmed by previous surgery [n=3] or frozen section [n=8])	LT	SLN followed by pelvic+paraaortic LND	Tc-99m+blue dye	-

SLN, sentinel lymph node; Op, operation; LND, lymph node dissection; LT, laparotomy; CH40, activated charcoal solution; Tc-99m, technetium-99m radiocolloid; LS, laparoscopy; ICG, indocyanine green; RB, robotic.
[a]Pilot study of SENTOV trial.
[b]Preliminary results of SELLY trial.
[c]SENTOV trial phase II.
[d]SONAR-2 trial phase I.

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Table 2. Summary of studies on the detection accuracy of SLN biopsies in patients with early ovarian cancer

Study	Tracer	Tracer dosage	Injection site	Injection time	Interval from injection to detection	SLN location	Detection rates	Sensitivity	NPV
Negishi et al. (2004) [10]	CH40 (activated charcoal solution)	0.05-0.2 mL	Ovarian cortex	Before adnexectomy	10 minutes	Paraaortic (91.0%) Common iliac (26.0%) External iliac (9.0%)	100.0%	-	-
Nyberg et al. (2011) [19]	Tc-99m+blue dye	19 MBq (0.9 mL)+2.0 mL	Ovarian hilum	15 minutes before adnexectomy	138 minutes	Paraaortic only (100.0%)	94.0%	-	-
Kleppe et al. (2014) [14]	Tc-99m+blue dye	20 MBq+0.2 mL-0.5 mL	Ovarian ligament & IP ligament	15 minutes before adnexectomy	50 minutes	Paraaortic only (67.0%) Pelvic only (9.0%) Pelvic/paraaortic (24.0%)	100.0%	-	-
Buda et al. (2017) [16]	ICG	0.5 mL-1.0 mL (1.25 mg/mL)	Ovarian ligament & IP ligament	Before adnexectomy	-	Paraaortic only (70.0%) Pelvic only (10.0%) Pelvic/paraaortic (20.0%)	90.0%	No positive node	100.0%
Angelucci et al. (2016) [25]	ICG	0.5 mL-1.0 mL (1.25 mg/mL)	Ovarian hilum	Before adnexectomy	2 minutes	Paraaortic only (40.0%) Pelvic only (60.0%)	100.0%	No positive node	100.0%
Hassanzadeh et al. (2016) [15]	Tc-99m+blue dye (used in 4 patients)	37 MBq (0.2 mL)+0.2 cc	Ovary cortex (n=10) Ovarian ligament & IP ligament (n=25)	10 minutes before adnexectomy	-	Paraaortic only (87.5%) Pelvic only (8.3%) Pelvic/paraaortic (8.3%)	40.0% 84.0%	NA 100.0%	-
Lago et al. (2019) [34]	Tc-99m+ICG	37 MBq (0.2 mL)+0.5 mL (1.25 mg/mL)	IP ligament stump±ovarian ligament stump[a]	After adnexectomy	15 minutes[b]	Paraaortic (70.0%) Pelvic (87.5%)	Both: 100.0% (Tc-99m alone: 100.0%), (ICG alone: 90.0%)	-	-
Uccella et al. (2019) [9]	ICG	2.0 mL (1.25 mg/mL)	IP ligament stump±ovarian ligament stump[a]	After adnexectomy[c]	5-20 minutes	Paraaortic only (62.0%) Pelvic only (19.0%) Pelvic/paraaortic (19.0%)	67.7% (immediate, 88.9%), (delayed, 41.7%)	100.0% (specificity 100.0%)	100.0% (PPD 100.0%)
Lago et al. (2020) [20]	Tc-99m+ICG	37 MBq (0.2 mL)+0.5 mL (1.25 mg/mL)	IP ligament stump±ovarian ligament stump[a]	After adnexectomy	15 minutes[b]	Paraaortic (100.0%) Pelvic (93.3%) Pelvic/paraaortic (95.0%)	Both: 100.0% (Tc-99m alone: 100.0%), (ICG alone: 95.0%)	No positive node	-

Table 2. Summary of studies on the detection accuracy of SLN biopsies in patients with early ovarian cancer (Continued)

Study	Tracer	Tracer dosage	Injection site	Injection time	Interval from injection to detection	SLN location	Detection rates	Sensitivity	NPV
Laven et al. (2021) [17]	Tc-99m+blue dye	20 MBq (0.15 mL)+2.0 mL	IP ligament stump+ovarian ligament stump	After adnexectomy[c]	15 minutes	Paraaortic only (67.0%) Pelvic only (0.0%) Pelvic/paraaortic (33.0%)	27.3%	No positive node	-

Values are presented as number (%).

SLN, sentinel lymph node; NPV, negative predictive value; CH40, activated charcoal solution; Tc-99m, technetium-99m radiocolloid; IP, infundibulo-pelvic; ICG, indocyanine green; NA, not available; PPD, positive predictive value.

[a]The tracer was injected into the ovarian ligament stump if there was no history of hysterectomy.

[b]Thirty minutes after injection, an SLN biopsy was performed.

[c]SLN biopsy was performed during immediate staging (patients who underwent SLN mapping immediately after oophorectomy) or delayed staging (patients who had previously undergone oophorectomy within 30 days).

3. Tc-99m

Alex and Krag introduced Tc-99m to patients with primary melanoma. Researchers have extensively reported their findings, using various radiotracers (including Tc-99m sulfur and sulfide) and lymphoscintigraphy, spanning from the preoperative localization and labeling of major lymph channels and LNs to the intraoperative use of gamma-detecting probes for SLN localization [13].

The exposure of Tc-99m radiation to surgeons, theater nurses, and pathologists during SLN biopsy did not exceed the safe limit (500 procedures/person/year) [14]. However, it is noteworthy that this tracer requires a long time for absorption from the ovarian lymphatics. Both preoperative (such as radiology department availability) and intraoperative (including handheld gamma cameras for lymphoscintigraphy to facilitate SLN localization) can prove to be cumbersome.

4. ICG

Since 1959, the United States Food and Drug Administration has approved ICG was approved for use in humans in various medical settings. ICG has emerged as a promising tracer for SLN mapping in vulvar, cervical, and endometrial cancers. ICG tracer detection requires near-infrared real-time fluorescence imaging, with the SLN defined as an area of higher gain than the background. Numerous studies of gynecological malignancies have consistently demonstrated the safety and efficacy of ICG as a tracer for SLN mapping. One of the primary advantages of ICG is that it obviates the need for preoperative preparation with tracers such as radioactive colloids, which can pose logistical and safety challenges. Therefore, ICG is a highly convenient option for SLN mapping in gynecological malignancies.

Variations in the detection rates were observed depending on the choice of agent, either alone or in combination (Table 3). Although the same agent was used as a tracer, differences in injection site, timing, and other study protocols appeared to have affected the results. Notably, both studies using a combination of Tc-99m and ICG as tracers showed a detection rate of 100.0%. It can be predicted that SLN mapping using the advantages of these two agents as tracers will increase the detection rate. Therefore, recent early OC SLN studies have attempted to use combination tracers. However, since various agents have been previously used as SLN tracers in cervical and endometrial cancers, ICG is mostly used. To standardize the tracer, further studies are necessary to

Table 3. Sentinel lymph node detection rates according to tracer agents

	No. of studies	Range of detection rate (%)
Alone		
ICG	3	67.7-100.0
CH40	1	100.0
Blue dye	-	-
Tc-99m	-	-
Combination		
Tc-99m+blue dye	4	27.3-100.0
Tc-99m+ICG	2	100.0

ICG, indocyanine green; CH40, activated charcoal solution; Tc-99m, technetium-99m radiocolloid.

compare the accurate detection rate of each agent using the same protocol.

5. Injection site

The infundibulopelvic (IP) and ovarian ligament stumps were the most preferred injection sites (Table 2). Only four studies administered injections into the ovarian cortex, or hilum.

6. Ovarian cortex

Ovarian cortex injection for SLN mapping is associated with the potential risk of tumor cell spillage and dissemination. In a study by Hassanzadeh et al. [15], subcortical injection of Tc-99m for SLN mapping was technically challenging and had a low detection rate of 40.0% when using a radiotracer. Furthermore, this method cannot be repeated in the same location, regardless of the ovarian mass size, and cannot be performed in patients undergoing re-staging surgery after oophorectomy. Several studies have explored alternative injection sites, including the ovarian ligament, the ovarian suspensory ligament, and the ovarian hilum, to improve the efficacy and safety of SLN mapping in gynecological malignancies.

7. IP ligament (or ligament stump) and ovarian ligament (or ligament stump)

Compared to the ovarian cortex, the IP ligament (or ligament stump) and ovarian ligament (or ligament stump) appear to be safe and reproducible injection sites (Fig. 1). The tracer is usually injected into the dorsal and ventral sides of the ovarian and IP ligaments [16]. The detection rate ranged from 27.3-100.0%. A study by Laven et al. [17], which used a combination of Tc-99m and a blue dye, showed the lowest
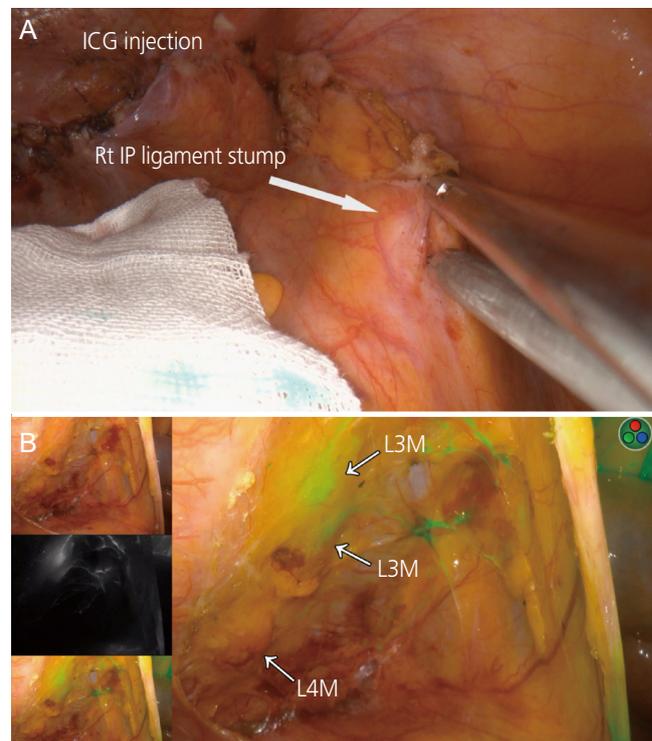

Fig. 1. Single-port assisted laparoscopic indocyanine green (ICG) injection at infundibulo-pelvic (IP) ligament stump. (A) ICG tracer injection at right IP ligament stump; (B) sentinel lymph node identification. Rt, right; L3M, inframesenteric aortocaval; L4M, supramesenteric aortocaval area.

detection rate. Except in this study, injections at these sites showed detection rates ranging from 67.7-100.0%.

In a recent prospective observational study, Uccella et al. [18] investigated the pelvic SLN concordance rate at two injection sites, the utero-ovarian ligament and cervix, in each hemipelvis, using different tracers (ICG at the cervix and

methylene blue at the utero-ovarian ligament). The two injection sites appeared to map to the same SLN with higher probability. This suggests that cervical injection could be an alternative to ovarian ligament injection for SLN mapping in patients with early OC [18].

8. Injection time: before or after tumor resection

Although Nyberg et al. [19] reported that the time interval between tracer injection and SLN detection tended to be longer in patients with a higher body mass index (BMI), Uccella et al. [18] reported no significant difference in BMI between the successful and unsuccessful mapping groups (P=0.894). Additionally, we found no significant differences in age, comorbidities, histology, OC grade, or surgical staging method (laparotomy, laparoscopy, or robotic) between the successful and unsuccessful groups.

However, patients in the delayed staging group (defined as patients who underwent re-staging after oophorectomy within 30 days) showed significantly lower detection rates than those who underwent immediate staging (defined as patients who underwent SLN mapping immediately after oophorectomy) (88.9% vs. 38.5%) [9]. This difference was also observed in a study by Laven et al. [17] (SLN detection rate: 37.5% in primary surgery vs. 0.0% in delayed surgery between 5 and 8 weeks after primary surgery). In a study by Lago et al. [20], the tracer was injected into the ovarian and IP ligament stumps if the surgically removed tumor specimen (ovary) was confirmed to be malignant in the frozen section. In addition to the issue of differences in the tracer, the SLN detection rate was not inferior when compared with other studies that injected the tracer before tumor resection [14,16,20]. These results suggest changes and reconstruction of the lymphatic drainage system after tumor resection. That is, when tracer injection was performed immediately after adnexectomy, the SLN detection rate did not differ according to the tracer injection timing (before or just after adnexectomy). Tracer injection before histological confirmation is accompanied by ethical issues, the risk of complications, and additional costs associated with the procedure. In consideration of this, the tracer was injected before tumor resection in the first six studies of this review but was injected after histologically confirming malignant tissue by frozen section after tumor resection in the following four studies.

9. SLN location

Metastasis from OC can occur via three different pathways (transcoelomic, hematogenous, or lymphatic) [21]. The lymphatic route has three lymphatic drainage systems. The main route runs along the ovarian vessels and terminates at the aortic node, near the renal vessels. The second route runs within the broad ligaments and terminates at the external iliac and interiliac nodes. The second route reaches the common iliac and aortic nodes. The third route drains through the round ligament, reaching the external iliac and inguinal nodes. The incidence of LN metastasis is 10.0-15.0% in ovarian-confined OC, and 64.0-67.0% in advanced OC. In patients with nodal metastases, up to 50.0% of the LN metastases are located in the paraaortic area [22].

In this review, the SLN locations were grouped into three regions: para-aortic only, pelvic only, and both pelvic and para-aortic (pelvic/para-aortic) (Table 2). The detection rates of each region were 40.0-100.0%, 0.0-60.0%, and 8.3-33.3%, respectively. The para-aortic area appears to be the most common location of ovarian SLNs that drain through the IP ligament [23,24]. Nyberg et al. [19] reported that left ovarian SLNs were mostly (64.0%) located above the inferior mesenteric artery (IMA), whereas right ovarian SLNs were mainly located below the IMA (94.0%). Similarly, in other studies, left ovarian SLNs were found just below the renal vein, and right ovarian SLNs were mostly located below the IMA. Additionally, when OC is confined to a unilateral ovary, lymphatic metastasis seems to be limited to the ipsilateral side of the injection site and is less likely to be located on the contralateral or bilateral sides [9,10,14,16,18,25,26]. However, other studies have reported only a few cases of contralateral node involvement in patients with early OC [22,27]. These data imply that further investigation of ovarian lymphatics is necessary to improve the SLN detection rate in early OC.

10. Ultrastaging and detection accuracy of SLN

Practically, SLN biopsy allows for a more comprehensive pathological evaluation, a challenge with conventional lymphadenectomy. Ultrastaging, enabled by the examination of a small number of 'high-risk' LNs enhances the detection of LN metastasis, typically in cases of low-volume disease. In essence, ultrastaging improves the diagnostic accuracy of SLN biopsy for early OC. LN metastasis was categorized as macrometastasis (foci of metastasis greater than 2 mm), micrometastasis (0.2-2 mm), or isolated tumor cells (less

Table 4. Characteristics of clinical trials investigating the sentinel lymph node in ovarian cancer

Study (trial registration number)	Estimated enrollment	Tumor type/ stage	LND protocol	Injection site	Injection time	Tracer	Tracer dosage	Ultrastaging
SONAR-2 (NCT02540551) [19][a]	11 (actual enrollment)	Ovarian cancer (confirmed by previous surgery [n=3] or frozen section [n=8])	SLN followed by pelvic+paraaortic LND	IP ligament stump+ovarian ligament stump	After adnexectomy (immediate or delayed)	Tc-99m+blue dye	20 MBq (0.15 mL)+2.0 mL	-
SENTOV (NCT03452982) [20,29,34][b]	20	Ovarian cancer (confirmed by previous surgery or frozen section)	SLN followed by pelvic+paraaortic LND	IP ligament stump±ovarian ligament stump (if no previous hysterectomy)	After adnexectomy	Tc-99m+ICG	37 MBq (0.2 mL)+0.5 mL (1.25 mg/mL)	-,Afterwards, ultrastaging was performed in pilot study and clinical trial patients Regular intervals of 200 μm, with a limit of 6 levels If absence of metastasis, IHC (anticytokeratin AE1:AE3)
SELLY (NCT03563781) [9]	176	Early epithelial ovarian cancer/ I–II	SLN followed by pelvic+paraaortic LND	IP ligament stump±ovarian ligament stump (if no previous hysterectomy)	After adnexectomy (immediate or delayed)	ICG	2.0 mL (1.25 mg/mL)	+,The negative ones are ultrastaged following a protocol based on multiple H&E sections combined with IHC (anticytokeratin AE1:AE3)
MELISA (NCT05184140) [35][c]	62	Ovarian mass (suspicious of malignancy), ovarian cancer (re-staging)	Malignant cases, SLN followed by pelvic+paraaortic LND	IP ligament stump±ovarian ligament stump	Tc-99m injection (preoperative)+ ICG injection (after adnexectomy when frozen section proven malignancy)	Tc-99m+ICG	37-74 MBq (0.4 mL/ injection)+0.3 mL–1.0 mL (2.5 mg/mL)	+,4 μm thick, regular intervals of 150 μm, performing 4 levels of each paraffin block If absence of metastasis, IHC (anticytokeratin AE1:AE3)

LND, lymph node dissection; SLN, sentinel lymph node; IP, infundibulopelvic; Tc-99m, technetium-99m radiocolloid; ICG, indocyanine green; IHC, immunohistochemistry; H&E, hematoxylin and eosin.
[a]Terminated due to low detection rate.
[b]Completed.
[c]Recruiting.

than 0.2 mm) [9]. Conventional pathological studies (single section and hematoxylin and eosin staining) failed to detect micrometastases and isolated tumor cells; they were mainly detected by ultrastaging. However, no standardized ultrastaging protocol has been established for SLN in gynecological cancer [15,28].

Uccella et al. [9] reported four cases with SLN positivity (12.9%, one case of isolated tumor cells and three cases of macrometastasis) with no cases of false-negatives or false-negative SLNs using the ultrastaging technique. Comprehensive para-aortic/pelvic LN dissection was performed for validation, resulting in the upstaging of three patients after surgical staging. Their study also presented preliminary report from the SELLY trial, indicating successful identification of all metastatic nodes in the SLN. These results imply that if performed correctly, SLN detection could serve as a precise and reliable nodal assessment method [9]. In another study, Lago et al. [29] performed ultrastaging in the SENTOV pilot trial and clinical trial patients; two patients were upstaged to stage IIIA1 due to LN metastasis. In the first case, pelvic SLN micrometastasis was upstaged to macrometastasis (1-2.1 mm) using an ultrastaging protocol. In the second case, para-aortic macrometastasis occurred in a patient whose SLN was not accessed in the para-aortic area because of SLN mapping failure with an IP ligament injection [29].

However, the clinical significance of isolated tumor cells and metastasis has not yet been identified. For breast cancer, isolated tumor cells or micrometastases among patients with early stage breast cancer who do not receive adjuvant treatment are associated with a worse prognosis [30]. Conversely, in endometrial cancer, the adverse effects of micrometastases and isolated tumor cells on prognosis remain uncertain [31,32]. Further research is necessary to elucidate the prognostic significance of micrometastases and isolated tumor cells in early OC as well as the establishment of a standardized ultrastaging protocol.

11. Complications associated with SLN biopsy

Among the studies included in this review, a few complications related to SLN biopsy have been identified. In most cases, patients with previous allergic reactions to tracer agents were excluded from the study. The only reported adverse effect associated with the tracer agent was immediate hypersensitivity reaction to the use of blue dye. Immediate-type hypersensitivity (hypotension and urticaria in the left arm)

was observed 15-20 minutes after the blue dye injection. The patient required several intravenous doses of etilefrine, hydrocortisone, and alongside infusion of norepinephrine [18]. No allergic or adverse reactions were observed with other tracer agents. Another reported intraoperative complication was superficial injury to the vena cava during SLN biopsy, which was successfully repaired through laparoscopic suture as detailed in the study by Buda et al. [16]. A few cases of postoperative complications were recorded, including ileus and vaginal dehiscence; however, most did not appear to have a direct correlation with the SLN biopsy technique [20].

12. Perspectives for future research

Several clinical trials have been conducted to explore the efficacy of SLN biopsy for early OC (Table 4). Most of these studies utilized a combination of Tc-99m with blue dye or ICG as a tracer, which were injected into the IP and ovarian ligaments. However, in the SELLY study exclusively employed ICG for SLN mapping. In early studies, ultrastaging was not a standard practice; however, both the later SELLY and MELISA studies incorporated ultrastaging techniques to detect low-volume diseases. Furthermore, a single-center prospective phase 3 trial evaluated the non-inferiority of ICG compared to Tc-99m in SLN biopsy for various cancers (including breast, skin, ovary, vulva, and anal cancer) as part of the GASVERT trial (NCT02997553).

With the advancements in minimally invasive surgery, studies on SLN biopsies in various cancers are promising [33]. Although the current body of research on SLN biopsy in early ovarian cancer is relatively limited, the potential importance of future investigations in this area should not be underestimated. Given the potential benefits of SLN biopsy for accurate staging and therapeutic decision-making, further studies in this field hold significant promise for improving patient outcomes.

Conclusion

The clinical utility of SLN biopsy in early stage OC remains uncertain due to limited evidence in the literature. In addition to accuracy and reliability issues, technical difficulties associated with ovarian SLN biopsy also present obstacles to the widespread utilization of this technique. It requires experienced surgeons with a comprehensive understanding of

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lymphatic flow from the ovary. Furthermore, early stage OC is rare, posing challenges in recruiting a sufficient number of patients for clinical trials. Nonetheless, the motivation for studying SLN biopsies in early OC stems from the limited sensitivity of preoperative imaging tests in detecting LN metastasis. Therefore, surgical nodal assessment of OC is crucial to determine the exact stage of the patient, thereby facilitating appropriate adjuvant treatment. SLN biopsy in early OC could reduce morbidity and complications compared with comprehensive lymphadenectomy in conventional staging. Further research is required to establish the clinical significance of SLN biopsy in early stage OC.

Conflict of interest

The authors declare no conflicts of interest.

Ethical approval

Not applicable.

Patient consent

No patient consent is needed for this review article.

Funding information

None.

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