The Role of Sentinel Node Dissection

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Petra Zusterzeel, Annemijn Aarts, Jenneke Kasiu, and Tineke Vergeldt

Hysterectomy with bilateral salpingo-oophorectomy and complete surgical staging by lymph node dissection has been recommended as the standard of care for apparent early-stage endometrial cancer in many national guidelines since 1985 [1]. Other, mainly European, guidelines include neither a lymph node dissection nor lymph node sampling. Whether to perform a lymph node dissection has been one of the most controversial areas in the management of endometrial cancer. Moreover, the extent of the lymph node dissection is of ongoing debate, such as pelvic versus pelvic and para-aortic; below versus above the inferior mesenteric artery; complete lymphadenectomy versus lymph node sampling.

Lymph node status is the most important predictor of survival. Surgical staging with lymphadenectomy defines recurrence risk and guides postoperative treatment planning [2, 3]. Proper surgical staging provides information on the actual extent of disease rather than on perceived risks based on uterine factors, such as grade, histology, and depth of myometrium invasion. However, two randomized controlled prospective European trials evaluating the role of lymph node dissection in early-stage endometrial cancer demonstrated no impact on survival [2, 4, 5].

The ASTEC (A Study in the Treatment of Endometrial Cancer) trial was a multicentre prospective study in which 1308 patients with clinical stage 1 disease were randomized to either a hysterectomy with bilateral salpingo-oophorectomy or standard treatment with lymph node dissection. After a median follow-up of 37 months no differences in disease-free and overall survival were noted between the two arms.

There is increasing awareness of the long-term side effects of lymphadenectomy such as lymphocyst formation, neurovascular injury, and leg lymphedema. Furthermore, complete pelvic and para-aortic lymphadenectomy can be technically

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challenging, time-consuming, contributes to peri-operative bloodloss, and is not feasible in a significant number of patients because of body habitus and comorbidities. On the other side, when surgical staging is inadequately or not performed at all, patients can be subjected to unnecessary adjuvant treatment, such as pelvic radiation therapy, and its associated side effects [6].

Based on the current standard of treatment, surgeons are faced with the dilemma of "understaging" versus "overtreating."

The use of sentinel lymph node (SLN) mapping in endometrial cancer may be an acceptable solution, providing a middle ground between complete lymphadenectomy and no nodal evaluation.

Although initially described by Gould et al. in 1960 [7], lymphatic mapping did not garner much attention over the ensuing decades in endometrial cancer. SLN mapping is an image-guided procedure that is well established in the treatment of cancers, such as melanoma, breast, and vulva [7–9]. A SLN is defined as the first node to receive drainage from a primary tumour and is most likely to harbor metastases in cancers with lymphatic spread. If the SLN is negative for metastasis, then the ensuing lymph nodes should also be negative. SLN mapping may also detect aberrant lymphatic drainage that would be missed on routine lymph node dissection. A recent study showed that SLN in endometrial cancer patients are three times more likely than non-SLN to harbor metastatic disease [10].

12.1 SLN Mapping Technique: Where to Inject

If SLN biopsy is introduced to the standard clinical care in early-stage endometrial cancer, a consensus should be reached on the most accurate method to perform this procedure. At this time, however, several different techniques have been described and used, including a variety of injection sites and tracers.

One of the main discussion points concerning the procedure is the injection site. In tumors in which SLN biopsy is already frequently used, such as melanoma, breast, and vulva, the tracer is injected around the tumor itself, to access the lymphatic channels draining the tumor. The major obstacle in endometrial cancer is the fact that the uterine corpus is an internal structure and that the tumor is encased within this smooth-muscle organ. This makes peritumoral injection more difficult.

There are three injection sites described in the lymphatic mapping of endometrial cancer: the uterine corpus (subserosal/myometrial), the cervix, and the endometrium via hysteroscopy. By injecting the uterine cervix or the fundus, the lymphatic channels of the organ and not specifically that of the tumor are detected [11]. It remains unclear if cervical injection leads to the identification of the SLN that is representative of the location of the endometrial tumor [12]. Some investigators have injected the fundus to look for the lymphatic channels that follow the ovarian vessels and have routinely found sentinel nodes (SN) along the aorta up to the level of the renal vessels. Nonetheless, this fundal injection approach ignores the

important cervical channels that also drain a primary endometrial cancer [13]. By using a hysteroscope to visualize the actual tumor, tracers can be injected peritumorally. In a study using this technique, SN in both the pelvis and the para-aortic region were found [14], but with a low detection rate [15]. Besides that, one of the theoretical concerns when performing hysteroscopic injection in patients with endometrial cancer is the risk of disseminating malignant cells through the fallopian tubes [16].

Although there has been a concern that the nodal spread patterns are different between different injection sites, a meta-analysis published in 2011 showed that cervical injection was not inferior to other methods. Subserosal injection as the only injection site was not advised because it may decrease sensitivity of SLN biopsy [17]. Reasons to choose cervical injection is the accessibility and the fact that the cervix is rarely distorted by anatomic variations, such as myomas, in women with endometrial cancer. A combined superficial (1–3 mm) and deep (1–2 cm) cervical injection has been described as adequate [18].

12.2 SN Mapping Technique: Which Tracer to Use

There are three methods described for the detection of SLN: colorimetric blue dye, radioactive isotopes, and fluorescent indocyanine green (ICG) dye.

Commonly used blue dyes include isosulfan blue, blue violet, and methylene blue. The blue dye is injected in the operating room while the patient is under anesthesia. Visualization of blue-stained lymphatic channels and lymph nodes follows shortly after injection in normal white light. The interval from injection to detectable SLN is approximately 10–20 min. Extended delay between injection and dissection of SLN may result in more diffuse staining of the lymphatic bed and thus increased difficulties in detecting SLNs [19].

Radioactive tracers contain technetium-99m (Tc-99m) radioisotope bound to nanoparticles like colloidal Sulfur or human albumin. This is injected on the day of or 1 day prior to surgery. For detection of the SLN a preoperative scintigraphy can be made and/or an intra-operative handheld gamma probe can be used. In contrast to blue dye, radioisotopes are costly and require more logistic efforts and preparation [16].

More recently, the feasibility of a new near infrared (NIR) fluorescence imaging system using ICG has been described for the purpose of SLN mapping. ICG dye is injected in a similar fashion to that of blue dye but is visualized with a NIR imaging camera. The SLN detection rates with ICG and the bilateral SLN detection rates appear comparable or better than those of blue dye only or Tc-99 m [18, 20].

Studies combining dye with radioactive tracers in endometrial cancer have shown variable results. In a prospective study in 2017, the addition of ICG and NIR imaging to blue dye detected significantly more SLN and detected more metastases than the use of blue dye alone [21]. The combination of blue dye and ICG with NIR

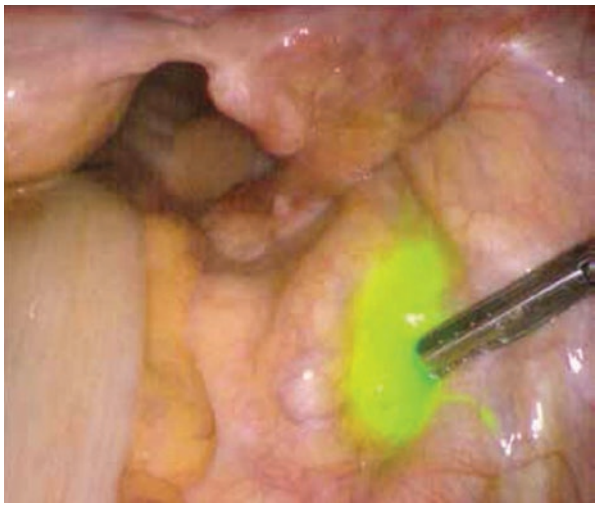

Fig. 12.1 SN procedure with ICG

Table 12.1 Detection rate of different tracers in studies including >100 patients

Tracer	Overall detection rate	Bilateral detection rate
Blue dye alone	71% [How]	43% [How]
	84% [Khoury-Collado]	67% [Khoury-Collado]
	81% [Barlin]	
	86% [Desai]	52% [Desai]
Tc-99 alone	88% [How]	71% [How]
ICG alone	87% [How]	65% [How]
	95% [Jewell]	79% [Jewell]
Blue dye + Tc-99	88% [Naoura]	63% [Naoura]
	75% [Frati]	37% [Frati]
Blue dye + ICG	*No data*	84% [Holloway]
Tc-99 + ICG	*No data*	*No data*

imaging had high sensitivity for the detection of lymph node metastasis, and conversely, a low false-negative rate, with no safety issues related to the use of ICG dye or the NIR imaging system (Fig. 12.1).

The detection rates of different tracers described in studies including more than 100 patients is shown in Table 12.1.

12.3 Where to Find the SLN

12.3.1 Lymphatic Drainage of the Uterus

The ideal SLN approach must be based on lymphatic anatomy. Three possible uterine lymphatic pathways are identified so far: the upper paracervical pathway (UPP), the lower paracervical pathway (LPP), and the infundibulo-pelvic pathway (IPP) [22] (Fig. 12.2).

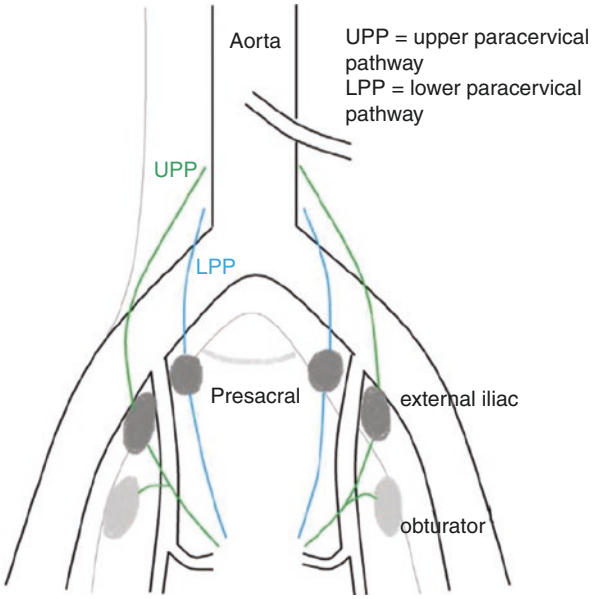

Fig. 12.2 The most common SLN position per lymphatic pathway in endometrial cancer patients [22]

The UPP runs along the uterine artery to drain—whether or not via the obturator lymph nodes—in the external iliac lymph node region. From the external iliac artery, the drainage route continues laterally via the common iliac artery to the precaval and para-aortic regions. The second pathway, the LPP, courses along the upper rim of the sacrouterine ligament towards the hypogastric and presacral region medial of the internal iliac artery. Via the internal iliac artery or presacral region, the drainage route continues medial to the common iliac artery and the precaval and para-aortic regions. The UPP and LPP seem to only be connected via fine lymphatic vessels in the cardinal ligament and function as separate, noncommunicating pathways from there onwards. In addition to the most common, pelvic pathways, the third pathway, the IPP, is the drainage route along the fallopian tube and the upper broad ligament via the infundibulo-pelvic ligament directly to the para-aortic lymph node region. As the UPP and LPP drain via the pelvis towards the lower para-aortic and precaval lymph node regions, it is suggested that a lower inframesenteric para-aortic dye positive lymph node can only be interpreted as the sole SLN in case no pelvic SLN are detected.

It remains undetermined if the uterine lymph drainage is effectuated by one SLN per hemi-pelvis or one SLN per hemi-pelvic drainage pathway. Moreover, anatomical variance between patients is probably a factor that influences the lymphatic pathway and thereby the SLN location(s).

12.3.2 SLN Location

Most SLN are located in the pelvis. Over one half of the SLN were found to be detected along the upper paracervical pathway, in the external iliac and obturator lymph node region [23, 24] (Fig. 12.3).

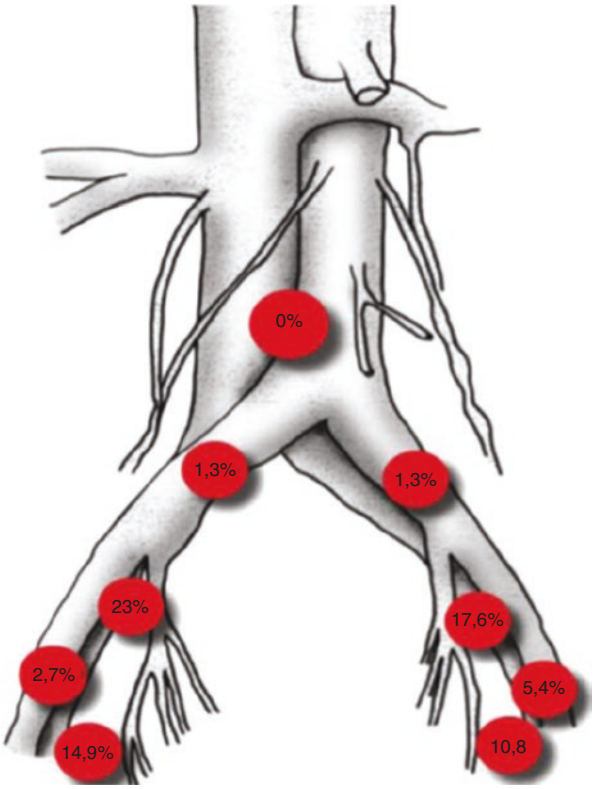

Fig. 12.3 Distribution of removed blue SLNs [24]

12.3.3 SLN Detection Rate

Data on the percentage of patients in whom one or more SLN are detected varies widely. Defined as the detection of at least one SLN per patient, the overall detection rate was described to be 81% (95% CI 77–84%) [19]. The bilateral detection rate, defined as the detection of at least one SLN on each hemi-pelvis of one patient was reported to be 50% (95% CI 44–55%). Finally, the detection rate of precaval or para-aortic SLNs, defined as the percentage of patients in whom at least one precaval or para-aortic SLN was detected, was found to be lowest, 17% (95% CI 11–23%).

Factors that were found to affect the SLN detection rate were the injection site and the used dye [19]. Patient characteristics such as BMI or surgical approach and tumor characteristics such as type of histology and grade did not significantly influence the SLN detection rate.

12.3.4 The Algorithm

To generate a reproducible, practical, and oncological safe SLN mapping approach, a SLN algorithm was developed by the Memorial Sloan-Kettering Cancer Center. The algorithm was first described in 2012 and extents the removal of dye positive

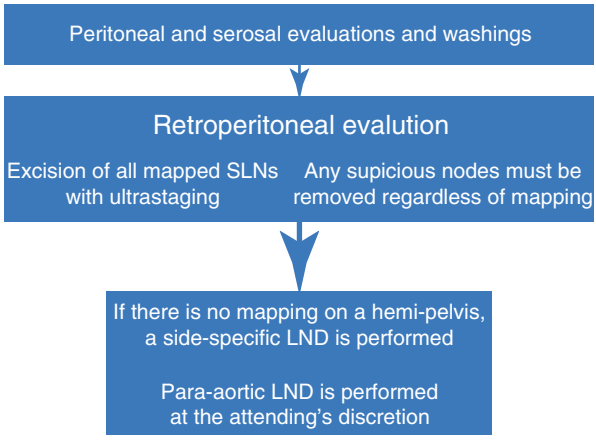

Fig. 12.4 SLN mapping algorithm [18]. *LND* lymph node dissection

lymph nodes [25]. The algorithm includes three main steps as shown in Fig. 12.4. First, the peritoneal and serosal surfaces need to be evaluated and washed. Second, the retroperitoneum must be evaluated. The dye positive lymph nodes need to be removed, as well as all other suspicious nodes, even if these lymph nodes are dye negative. Third, in case no SLNs are detected, a full lymph node dissection needs to be executed of the side-specific hemi-pelvis. The algorithm does not account the performance of a precaval and para-aortal lymph node dissection, which could be interpreted as an algorithm limitation in the rare occasion of isolated precaval or para-aortal lymph node metastases.

12.3.5 The Diagnostic Accuracy of SLN Mapping and the Effect of the Algorithm

To determine the diagnostic accuracy of a SLN procedure the histology of the SLN is assessed in relation to the histology of a pelvic lymph node dissection, whether or not combined with precaval and para-aortal lymph node dissection. The diagnostic accuracy can be calculated by three different approaches. First, the patients in whom the SLN cannot be identified can be categorized as false-negative. As the detection rate represents part of these data, this approach is least used. Second, without application of the algorithm, a hemi-pelvis in which the SLN cannot be found but a suspected lymph node contains the metastasis is accounted for as false-negative. According to the third approach, with use of the algorithm, the same hemi-pelvis will be accounted for as true positive as the suspected lymph node would have been dissected. Therefore, the diagnostic accuracy of a SLN procedure differs, mainly depending on the usage of the algorithm or not.

Without application of the algorithm, the sensitivity of SLN mapping is defined as the percentage of patients with at least one positive SLN divided by the patients with successful SLN mapping and lymph node metastases. This was reported to be 96% (95% CI 93–98%) [19]. The negative predictive value was 99.7%. Moreover, the SLN turned out to be the only lymph node containing metastasis in 60–66% of

all cases [19, 23]. The specificity of the SLN will always be 100% as a false-positive SLN is not possible.

The algorithm-specific sensitivity is defined as percentage of patients with at least one positive lymph node dissected according to the rules of the algorithm divided by the patients with lymph node metastases. Barlin et al. reported the first data on the effect of the algorithm on the diagnostic accuracy of the SLN procedure [25]. In 401 of the 498 patients at least one SLN was detected. The accuracy of the SLN mapping was assessed according to the two different approaches: sole removal of the SLN or removal of the lymph nodes by the rules of the algorithm. The sensitivity, negative predictive value, and false-negative rate were 85.1%, 98.1%, 14.9% and 98.1%, 99.8%, 1.9%, respectively. An increase in the diagnostic accuracy of SLN mapping using the algorithm has been confirmed by many other authors, even up to a sensitivity of 100% [26].

Specific attention has been given to detection of a SLN in the precaval or para-aortic lymph node regions in absence of SLNs in the pelvic regions [26]. Overall, two-third of the articles mentioning this topic reported that these isolated para-aortic SLN never occurred. The incidence in the remainder rated generally <5%. Moreover, the incidence of lymph node metastases in high-risk patients were found to be isolated to the precaval or para-aortic lymph node regions in 16% [27].

12.4 Role of Pathologic Ultrastaging

In SN procedures the pathologic technique plays an important role, as the SLN is the main and only tissue evaluated for metastasis. In addition, detection of micrometastasis (MMs) has appeared to be an important prognostic factor in different types of cancer [28, 29] and accounts presumably also for endometrial cancer [30]. There is significant evidence that micrometastases in lymph nodes are associated with recurrence of endometrial cancer [31]. Consequently, the pathologic technique used in SN procedures needs to have high detection rates and low false-negative rates. Pathological ultrastaging of lymph nodes is the most sensitive technique to meet the aforementioned requirements. This technique, using serial sectioning and immunohistochemistry (IHC), is therefore a main focus of the SN concept.

Definitions

- Macrometastasis—tumor cells larger than 2.0 mm.
- Micrometastasis—MMs—metastatic carcinoma in the form of microscopic clusters and single cells, measuring larger than 0.2–2 mm or less.
- Isolated tumor cells—ITCs—metastatic carcinoma in the form of microscopic clusters and single cells, measuring ≤0.2 mm.

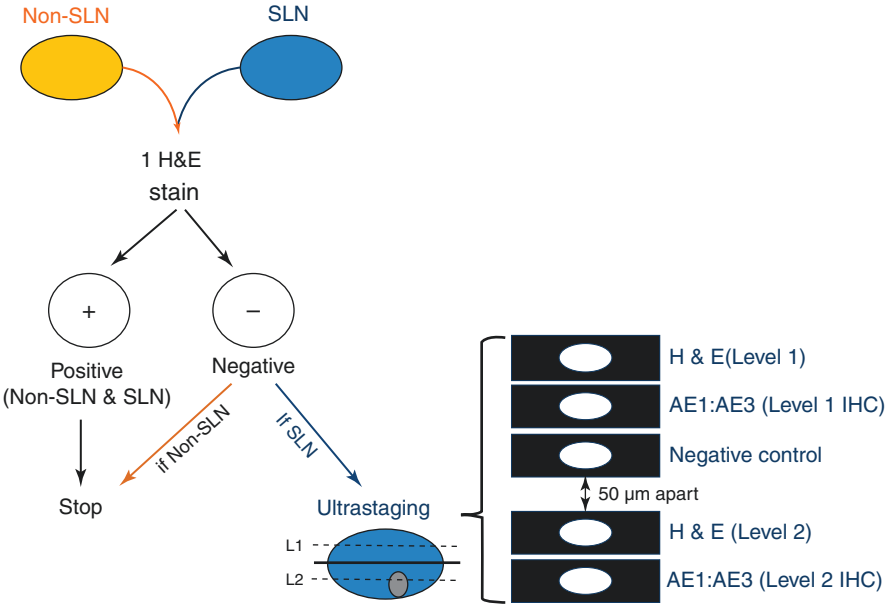

Fig. 12.5 Memorial Sloan-Kettering Cancer Center's pathologic ultrastaging algorithm for SLN. Source: International Journal of Gynecological Cancer 2013; 23(5):964–970

12.4.1 The Technique

Ultrastaging increases the ability to detect low-volume tumor cells as it reevaluates a presumed negative SLN at two additional levels with additional IHC stains. Ultrastaging protocols vary. Results depend on factors including the technique of serial sectioning and the antibodies used for IHC [31, 32]. In most studies assessing the sentinel procedure as part of operative staging of endometrial cancer, the following validated pathologic work up was used [32]. The ultrastaging algorithm is schematically depicted in Fig. 12.5. Only in case a SLN is negative, ultrastaging is applied. It is performed by dissecting the SLNs longitudinally in 4–5 µm section, 40–50 µm apart, perpendicular to the long axis of the node. These sections are stained with H&E and an additional section taken between the third and fourth levels are stained with IHC using the mouse monoclonal anti-AE1/AE3 cytokeratin [29, 33].

12.4.2 Sensitivity and Specificity of Ultrastaging

A meta-analysis of 17 trials with cervical cancer patients reported a 93% detection rate with H&E and IHC compared to 89.4% with H&E alone. This translates into a 96% NPV and 90% sensitivity [34]. For endometrial cancer, in the study by Kim

et al. [33] almost half of patients with positive SLNs had occult metastases, including MMs, which were not detected by conventional histology. More specifically, almost 13% of the 508 patients had positive nodes: routine H&E detected 35 patients (7%), ultrastaging detected an additional 23 patients (4.5%) who would have otherwise been missed. Six patients (1.2%) had metastatic disease in their non-SLNs. A 2008 patient series [35] found in almost 25% (10/46) of patients metastatic lymph nodes. In this study, three of the ten metastases corresponded to macrometastases and seven MMs. All the three cases of macrometastases and the three additional MMs were detected by H&E while three MMs were diagnosed by serial sectioning and IHC. A 2010 review, including six studies, showed that the rate of detection of MMs varied from 0 to 15% with a combination of H&E, serial sectioning, and IHC [31]. From 238 patients, 20% had lymph node metastases, including 6% with MMs.

In conclusion, in the performance of SN procedure for endometrial cancer ultrastaging leads to a higher detection and lower false-negative rate of macrometastases and MMs. This means that if the initial H&E staining is negative, then it is of major importance to also perform IHC.

12.5 Clinical Relevance of MMs and Isolated Tumor Cells

The SN procedure including pathologic ultrastaging seems beneficial because of the increased detection of MMs and isolated tumor cells in pelvic and para-aortic lymph nodes. However, it depends on the clinical relevance with respect to prognosis of these positive nodes in order to decide whether adjuvant therapy is needed.

In breast cancer patients with nodal MMs, detected by SN procedures, it was repeatedly shown that recurrences occurred significantly more often than in patients without MMs [36]. The role of ITCs seems to point into the same direction. It is therefore suggested in most studies to adjust adjuvant therapy strategies for these patients. In early cervical cancer MMs also seem to play a role in risk of recurrence. For instance, a retrospective case series with 292 patients, treated by radical hysterectomy, included a group of patients who recurred in a median time of 37 months and a matched control group with no recurrences after 122 months.

MMs occurred tenfold more often in the group of patients who recurred (11/26 and 1/26 respectively). The relative risk was 2.44 (1.58–3.78) [37].

For vulvar cancer the clinical relevance and implications of finding MMs and ITCs is less clear and needs more research [38].

The relevance of MMs in endometrial cancer has not been determined yet. Two studies showed that MMs removal was associated with significant increase in recurrence-free survival (RFS) [39, 40]. Hundred percent of patients without MMs had a RFS of 36 months, while this was only 71% of patients with MMs ($p = 0.0004$). Both RFS and overall survival were statistically significantly inferior for patients having MMs. On the contrary, another study found no evidence of increased recurrence of endometrial cancer in patients with positive MMs [41]. All three studies had small sample sizes and combined low-, moderate and high-risk groups of patients. Particularly in the low and moderate risk groups more research is needed to facilitate

decision-making regarding the adjuvant therapy strategy. To date, the clinical relevance of ITCs in endometrial cancer is unknown.SENTI-ENDO study

Some observational retrospective studies evaluated whether the finding of MMs or ITCs during SN procedures impacted choice of adjuvant therapy. In the follow-up of the SENTI-ENDO study 30% of the patients with negative SLN received adjuvant pelvic radiation and 12.5% chemotherapy, compared to 79% receiving pelvic radiation and 50% chemotherapy for those with a positive SLN, including MMs. There was no difference in RFS among groups. Another small study found no impact on RFS when treating MMS with external beam radiation and those with negative SLN with vaginal cuff brachytherapy [42].

In conclusion, at present the clinical relevance of detecting MMs and ITCs in endometrial cancer is uncertain. Future studies should seek for clarification and the possible consequences for choice of adjuvant therapy.

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