

Evidence for a Potential Usefulness of Sentinel Lymph Node Biopsy as a Future Standard in the Management of Endometrial Cancer

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Introduction

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, with an increasing incidence. About 80% of women are diagnosed at an early-stage (limited to the uterine corpus), with a 5-year overall survival (OS) rate over 95%, but in 20% of the cases, it spreads to lymph nodes (LN) and regional organs. When LN is involved, the 5-year OS decreases to 60%. Surgery is the main treatment and staging procedure; the standard surgical management in EC (hysterectomy and bilateral adnexectomy) includes a bilateral pelvic and paraaortic lymphadenectomy [1].

LN status is the most important prognostic factor and is essential to guide appropriate adjuvant therapy [2,3]. The subgroup of patients who benefit the most from lymphadenectomy is difficult to be identified before surgery, due to the amplitude of variables associated with prognosis. Sentinel lymph node (SLN) mapping and ultrastaging, are techniques under validation, which may be able to avoid the morbidity of a standard lymphadenectomy with a negative predictive value (NPV) of 99% [4].

The SLN is defined as the first LN to receive lymphatic drainage from a tumour [5]. SLNB in EC has been reported for almost 20 years since Burke et al. introduced the method in 1996. Sentinel lymph node biopsy (SLNB) is a promising technique that is demonstrating to be a safe, feasible, more accurate and less morbid alternative than lymphadenectomy in EC staging [3,6,7]. SLNB represents a half way treatment between no evaluation of lymph-node status and a complete pelvic and paraaortic lymph node dissection, which is called a selective lymph node mapping [1,3]. Selective lymph node mapping of all suspected lymph nodes and those located in unusual lymphatic drainage is equivalent to a high precision lymphadenectomy [8]. A high precision lymphadenectomy of selected suspected lymph nodes and minimally invasive surgical approach will be the future evolution and aim of the sentinel lymph node biopsy technique.

Mainly potential advantages of SLNB are: Short learning curve, simplifies the surgical procedure, decreases mean

surgical time and decreases morbidity by removing just one or a few nodes instead of systematic lymphadenectomy.

The aims of the SLN procedure are: Identifying suspected or metastatic lymph nodes, localising nodes in unusual drainage and detection of small tumour volume disease with a low complication rate [6,9]. The accuracy of SLNB may explain relapses in patients falsely considered without nodal metastasis after lymphadenectomy [10].

In this brief editorial work we are going to review: The clinical value and indications of the SLNB, technical aspects of the procedure and potential future areas of improvement.

Clinical Value and Potential Indications of the SLNB

The position of the SLNB in EC management is actually being evaluated [9]. Although SLNB is a diagnostic technique, it still cannot be considered a treatment strategy in EC [10]. The National Comprehensive Cancer Network (NCCN) clinical guideline considers the SLNB in the surgical staging in early-stage EC; it is a category 3 recommendation because many NCCN member institutions do not routinely use the technique [9].

SLNB usefulness still remains to be proven in EC as no increased survival has been evidenced [10]. In the prospective multicenter SENTI-ENDO study, recurrence rate (RR) and disease-free survival (DFS) in metastatic- or negative-SLNs had no significant differences in a mean follow-up of 50 months [7,9].

Besides, the role of lymphadenectomy in endometrial cancer is still questioned. In SEPAL and ASTEC trials, patients with intermediate- or high-risk of recurrence benefit from lymphadenectomy by reducing the risk of death ($p < 0.001$), but can be safely omitted in low risk patients [10]. So SLN mapping, without lymphadenectomy, may be most appropriate for patients at low-risk for metastases, in which adjuvant therapy could be omitted [9]. The potential effect of an accurate SLNB in low-risk patients is diluted due to a low

proportion of patients with positive nodes (15%), improved since ultrastaging of the SL [1,11].

Recently, two randomised trials compared hysterectomy plus lymphadenectomy versus hysterectomy alone in early-stage EC, they concluded that lymphadenectomy increased morbidity without improving oncologic outcomes [1,3,5]. Therefore, if we assume that lymphadenectomy has a pure diagnostic role, SLNB is enough to identify patients at high-risk of recurrence who would benefit from adjuvant therapy [1].

Another potential indication of the SLNB is in patients with comorbidities such as obesity or patients in which a complete staging surgery including lymphadenectomy cannot be performed [9], in order to better select patients at risk who would benefit from adjuvant therapy.

Technical Aspects

The injection site is still controversial in EC, due to a complex uterine drainage and the various modalities of tracer injection [10]. The location of the endometrial tumour is determinant in disease dissemination. Lesions located in the uterine fundus drain right away to the paraaortic lymph nodes via the ovarian vein [1].

Several injection sites (cervical, myometrial or endometrial injections) and different approaches (hysteroscopic, laparoscopic or transvaginal) have been described in EC. All techniques have been tested in multiple studies and have shown usefulness [1].

Cervical injection is the modality most reported and the preferred method. It is easier to perform than corporeal injection but has very low paraortic detection rate (DR) 5% [1]. A combined injection procedure with a superficial (1-3 mm) and deep (1-2 cm) cervical injection had better results ($P=0.045$) and was 3 times more accurately in detecting nodal metastases, as Khoury-Collado et al. demonstrated [10,11]. How et al. published the highest DR 92%, performing a cervical injection, but same false-negative rate (FNR) (15%) as other injection sites [9,10].

Corporeal (myometrial/subserosal and endometrial/perilesional) injections seem to be more consistent with lymphatic drainage from the endometrium [3], with higher DR of paraortic SLNs (40%-45.5%) [12,13].

Different tracers have been shown to be useful. Standard of use is combined technique of Tc99m with MB. MB alone has a low DR, so it is not usually recommended. Recently, real-time fluorescence with ICG offers a novel tool to identify SLNs with higher DR and accuracy than the other tracers [1], suppressing the use of radiocolloid and MB [6,9].

According to the previous data commented, corporeal injection, or the use of ICG fluorescent dye, its application is recommended for those patients with a higher risk of paraortic node metastasis [8].

Anatomopathological assessment of SLN by ultra-staging is the most important step of SLNB technique. Ultrastaging was able to detect up to an additional 40% of metastatic-SLNs,

mainly low-volume disease (micrometastases - μ M or isolated tumor cells - ITC), and upstaged 5%-15% of patients [8,11], which could possibly have been missed by conventional histological analysis [6,9]. However, the clinical impact, appropriate management and prognosis in the presence of μ M or ITC in the SLN are unclear in EC [9]. Removal of all or the majority of suspected/metastatic nodes does not correlate with improved survival [7]. Patients with micrometastases trend to a lower OS and DFS ($P<0.05$) while ITC appears to have no an impact on survival [9].

Potential Future Areas of Improvement

SLN is a promising technique, but before introduction the SLNB as a standard of care in EC, it is necessary to clarify some items:

There is a lack of a standardized surgical procedure about the SLN technique in EC staging among researchers. Satisfactory SLN mapping in EC requires adherence to a surgical SLN algorithm [3]. The incorporation of the surgical algorithm proposed by the Memorial Sloan-Kettering Cancer Center in Barlin et al. article and application of the ultra-staging histological analysis, has significantly reduced the FNR (5%), increased sensitivity (S) (95%) and improved NPV (99%) of the technique; without compromising the DR of nodal metastases [6,8].

We need to focus investigations on identifying the best approach for tumor's lymphatic drainage, injection site and best tracer(s), in accuracy and detection rate.

It is necessary to establish a minimal learning curve and technical requirements to ensure proper performance of the technique. Until then, the technique should be performed in centres with an experienced team [9].

It is also necessary to know the best therapeutic approach and impact in the survival of women with nodal metastases, especially low-volume metastatic-SLNs [7,10].

There is no randomized clinical trial on SLNB in EC yet and many of the data analyzed to support SLN mapping are based on single-institution studies. Recent meta-analysis did not obtain meaningful conclusions due to a lack of uniformity in methodology. More evidence and uniform criteria are needed. Studies with a long follow-up to evaluate clinical impact and prognosis of the SLNB application instead of lymphadenectomy [3,8].

In conclusion, the incorporation of the SLNB technique in staging EC is feasible, but questions remain to be determined. Meanwhile, the evolution of SLN mapping in EC continues.

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