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Review Article

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Current landscape and future perspective of sentinel node mapping in endometrial cancer

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ABSTRACT

Endometrial cancer (EC) represents the most common gynecological neoplasm in developed countries. Surgery is the mainstay of treatment for EC. Although EC is characterized by a high prevalence several features regarding its management are still unclear. In particular the execution of lymphadenectomy is controversial. The recent introduction of sentinel node mapping represents the mid-way between the execution and omission of node dissection in EC patients. In the present review we discuss the emerging role of sentinel node mapping in EC. In addition, we discussed how type of tracers utilized and site of injection impacted on sentinel node detection rates. Future perspective regarding EC management are also discussed.

Keywords: Endometrial Neoplasms; Sentinel Lymph Node; Lymph Node Excision; Laparoscopy; Robotic Surgical Procedures

INTRODUCTION

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries. It is estimated that the incidence of newly diagnosed EC increased every year. In the United States its incidence has increased of more than 20,000 cases between 2007 and 2017 [1,2].

Owing to the high prevalence of this malignancy several features of EC are fully investigated. Clear guidelines suggested several types of preoperative workup, surgical as well adjuvant treatments [3]. However, we have to acknowledge that few aspects of its management are far to be clear. In particular, data supporting the execution of retroperitoneal staging are discordant [4]. Current available guidelines suggest that surgical procedure should be included evaluation of the pelvic and para-aortic nodes [4-6]. Identifying disease harboring in the lymphatic tissues have important implications: 1) lymphatic dissemination is generally the first site of extra-uterine spread in women affected by EC, 2) presence of extra-uterine disease is useful from a prognostic point of view, and 3) these data might drive the need of postoperative treatments.

Data regarding the therapeutic value of lymphadenectomy are discordant, thus highlighting the unmet needs on this issue. Several retrospective large and well-conducted studies showed

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potential benefit of lymphadenectomy in EC [7,8]. However, two independent randomized trials focusing on the role of lymphadenectomy in EC reported that the execution of lymphadenectomy increase morbidity and worse peri-operative outcomes for our patients, without impacting on long-term outcomes [9,10]. The ASTEC trial and the Italian trial from Benedetti Panici et al. [9], included more than 1,900 patients who were randomly assigned to have hysterectomy and bilateral salpingo-oophorectomy (BSO) plus lymph node dissection vs. hysterectomy and BSO alone. The cumulative results of these studies reported that lymphadenectomy did not improve disease-free survival (pooled hazard ratio [HR]=1.23; 95% confidence interval [CI]=0.96–1.58) and overall survival (pooled HR=1.07; 95% CI=0.81–1.43) [11].

However, some pitfalls arising from the study design of these 2 trials impose to interpret with caution this finding: 1) the high prevalence of low risk EC determinate a low prevalence of lymphatic disease, 2) the execution of pelvic lymphadenectomy alone without para-aortic dissection in most patients might determinate an half-way treatment in patients with lymphatic dissemination (especially for patients with skip metastases [about 5% of the population]), 3) the lack of difference in radiotherapy rate among patients who had lymphadenectomy vs. no lymphadenectomy, and 4) the low number of nodes yielded might reflect a low quality of care for some patients.

The results of the SEPAL trial underlined the role of the execution of para-aortic lymphadenectomy in EC [12]. According to the background they observed that para-aortic lymphadenectomy has not impact in low-risk EC, but it improves outcomes of patients with intermediate- and high-risk disease (International Federation of Gynecology and Obstetrics [FIGO] grade 1 and 2 tumor limited to the inner half of the myometrium with lymphovascular space invasion, FIGO grade 3 and/or non-endometrioid stage IA and IB tumor, stage IC<). However, also the SEPAL study has some limitations: 1) the retrospective study design, 2) the low prevalence of nonendometrioid EC, and 3) the relative median young age of the population studied [12].

Overall, this unclear situation represented the background to change the treatment of EC. On this basis, also thanks to technical and technological attempts and the growing and interesting experiences in other malignancies (e.g., breast cancer, melanoma) we assisted to a paradigm shift in our clinical practice. In fact, the adoption of sentinel node mapping represents the most important and innovative change in EC surgical treatment over the recent decades. In the present review we aimed to discuss: 1) the introduction of sentinel node mapping in EC, 2) how detection rate is influenced by various tracers utilized and site of injection, 3) the adoption of sentinel node mapping during minimally invasive surgery, 4) the comparison to full lymphadenectomy in terms of morbidity and oncologic outcomes; and 5) the role of ultrastaging and the valence of micrometastasis and isolated tumor cells detected in sentinel nodes are discussed as well.

THE INTRODUCTION OF SENTINEL NODE MAPPING IN EC

Following growing and intriguing experience in other specialties, in 1996 started the first pioneeristic experience in the use of sentinel node mapping in EC. Burke et al., reported the M.D. Anderson Cancer Centre experience reporting outcomes of 15 women having open abdominal surgical mapping of lymph nodes [13]. Blue dye (1.0 ml) was injected into the subserosal myometrium in three uterine sites: the superior midpoint of the fundus, 2 cm

inferiorly on the anterior wall, and 2 cm inferiorly on the posterior wall. Dye uptake into lymphatic channels was observed for 10 min. Deposition of dye into lymph nodes occurred in 10 cases (67%). The locations of these nodes included para-aortic sites in 12, common iliac in 6, and pelvic in 13. Microscopic nodal metastases to sentinel nodes were identified in 2 of 4 women with proven lymphatic spread [13].

Ten years after the first report only few pilot studies were published. While in the last decade (from 2007 to 2017), a significant increase in the number of studies occurred, particularly, focusing on sentinel node biopsy, with more than 300 papers published on this issue [14].

The Memorial Sloan Kettering Cancer Center group published one of the cornerstone papers on the role of sentinel node mapping in EC [15]. In 2012, Barlin et al. [15], reported prospective data of patients having lymphatic mapping for EC. The surgical algorithm (that was applied retrospectively) included: 1) peritoneal evaluation thorough inspection and washing, 2) retroperitoneal evaluation with excision of all mapped or suspicious nodes, 3) side specific lymph node dissection in case of no mapping into a hemi-pelvis, 4) para-aortic node dissection performed at the discretion of the attending surgeon. Almost 500 patients were evaluated. A least one sentinel node was identified in more than 80% of patients. Sentinel node mapping identified 40 out of 47 patients with nodal involvement (false negative rate: 15%). However, when they applied retrospectively this algorithm, false negative rate dropped to 2% [15]. Other experiences corroborated these data, providing the basis to the widespread diffusion of sentinel node mapping in EC patients [16-18]. Finally, the National Comprehensive Cancer Network (NCCN) guidelines approved the utilization of sentinel node mapping algorithm in EC, thus making this approach rapidly and commonly used in most clinical practice [19].

TRACERS UTILIZED FOR SENTINEL NODE MAPPING

Various tracers have been tested during sentinel node mapping procedures in patients with EC. The most commonly utilized tracers included: 1) technetium-99 radiocolloid (Tc-99m), 2) blue dyes (including methylene, isosulfan, and patent blues), and 3) indocyanine green (IGC).

Tc-99m should be injected prior to surgery (generally the day before) into a radio-protected setting. Tc-99m has a half-life of about 6 hours. A gamma-probe is needed to detect the signal emitted by Tc-99m. The detection of sentinel nodes thorough Tc-99m is based on audiometric signal (no visualization of colors). However, the execution of single-photon-emission computed tomography (SPECT-CT) might be useful to obtain more precise information regarding the location of sentinel nodes. Elisei et al. [20], observed that the execution of SPECT-CT is associated with a highest detection rate and bilateral mapping when compared with audiometric signal only [20].

Blue dyes are injected into interstitial spaces. They bind serum proteins and are picked up by lymphatic vessels. The major advantage in the utilization in blue tracers is that they do not required dedicated and often costly equipments [21].

IGC is composed by small particles that show florescence after they are visualized thorough a near infrared light (range, 700–900 nm). A dedicated optical system is needed to visualize drainage of IGC into the lymphatic vessels.

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Several studies compared the effectiveness of various tracers in terms of detection rates and bilateral mapping [21]. Overall, these studies agree that IGC is characterized by a higher overall and bilateral detection rates in comparison to other methods (even if they are combined [Tc-99m plus blue dye]) [21]. Moreover, the detrimental effects of body mass index (BMI) in sentinel node mapping are softened when IGC is used as a tracer [21-23]. In fact, although accumulating data underlined that increasing in BMI reduce sentinel node detection rate the fluorescent signal observed with IGC might overcome the shielding effect of the adipose tissue on the colorimetric signal [21-23]. Two independent studies published by Tanner et al. [22] and Eriksson et al. [23] suggested the detrimental effect of an increased BMI on sentinel node detection and the better sentinel nodes visualization when IGC was used in comparison to blue dye.

Another point deserving attention is that current literature agrees that IGC is characterized by a better safety profile in comparison to Tc-99m (that is a radioactive drug) and blue dyes (various adverse events are reported including skin necrosis) [24]. On the light of this evidence, although costly, IGC should be considered the preferred tracers for sentinel node mapping (especially in the setting of minimally invasive surgery). However, blue dye cervical injection is a 'low-cost,' safe, and satisfactory alternative procedure to point out sentinel lymph node of uterus drainage.

SITE OF DYE INJECTION: CERVICAL OR CORPORAL INJECTION?

The optimal injection site for patients with EC has been studied in several investigations but it is not yet established. Two types of injection have been currently investigated: into the uterine cervix and uterine corpus. Injections into the uterine corpus (into the subserosal tissue, deeper myometrial and hysteroscopically-guided peri-tumoral injections) are characterized by a higher probability to sentinel node identification into the para-aortic area. Cormier et al, in a systematic review on sentinel node mapping, compared data of 1,102 and 300 patients having cervical and corporal injection, respectively [25]. They observed that the overall detection rate after cervical injection ranged between 62% and 100%; while after corporal injection ranged between 73% and 95%. However, all large studies (including more than 100 patients) reported an overall detection rate higher than 80% [25]. Para-aortic node mapping was observed in 39%, 2%, and 17% of patients having corporal, usual cervical and deeper cervical injection, respectively [25].

Theoretically, peri-tumoral injection should be performed in order to achieve the real lymphatic drainage of the tumor [26]. However, hysteroscopic injection is often considered to be challenging; while, cervical injection is simple and less time wasting than other corporal injection methods. Moreover, if we considered sentinel node mapping useful in the detection patients with extra-uterine spread in order to drive postoperative adjuvant treatments, we have to consider that pelvic node mapping is enough in more than 95% of patients, being skin metastases a very uncommon condition in EC patients.

The ongoing prospective multicentric sentinel node in endometrial cancer (SNEC) trial will be clarify pro and cons of cervical vs. hysteroscopic injection in EC. This study randomized patients to have cervical vs. hysteroscopic injection of IGC. Primary endpoint measures are detection rate into the para-aortic area and bilateral mapping into the pelvis [26]. Secondary

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endpoint measure included operative time, surgery-related complications as well as survival outcomes [26]. However, we have to point out that although hysteroscopic injection might guarantees a more accurate visualization of tumor lymphatic drainage, cervical injection is simple and less demanding than hysteroscopic procedure. In fact, ease of use of a system is vitally important in practical operation and for its widespread adoption.

SENTINEL NODE MAPPING AND MINIMALLY INVASIVE SURGERY

The growing adoption of minimally invasive surgery for EC staging contributed to the increased popularity in sentinel node mapping. The adoption of innovative laparoscopic and robotic-assisted systems that include software for the identification of sentinel nodes represents one of the major advantages in this field [27]. Recently, the FIRES trial published by Rossi and colleagues corroborated these results [28]. The FIRES trial is a multicenter prospective cohort study focusing on 385 patients with apparent stage I EC undergoing robotic-assisted surgery. Patients included had hysterectomy plus sentinel node mapping followed by pelvic (with or without) para-aortic lymphadenectomy [28]. Mapping in at least one sentinel node was observed in 86% of cases. Positive nodes were identified in 41 patients (36 of those patients had at least one mapped nodes). Among this latter group of patients' nodal metastases were identified into the sentinel nodes in 35 cases (97%). According to these numbers, sensitivity to detect node-positive disease is 97.2% and the negative predictive value is 99.6% [28]. Therefore, it was observed that sentinel node mapping is highly effective during minimally invasive procedures. Thanks to the magnificent view of the laparoscope and innovative technological systems allowing to visualize various concentrations of the tracer, minimally invasive surgery rapidly becomes the gold standard method to identify sentinel nodes.

MORBIDITY RELATED TO SENTINEL NODE MAPPING AND FULL LYMPHADENECTOMY

The execution of sentinel node mapping instead of full lymphadenectomy (pelvic ± para-aortic) reduces the occurrence of peri-operative morbidity [29]. In fact, the execution of full lymphadenectomy might determinate the occurrence of several peri-operative events including also lymphatic-specific complications. These complications included the occurrence of lymphoedema, lymphorrhea, and lymphoceles.

Although the introduction of minimally invasive surgery minimizes the occurrence of lymphatic complications dramatically they still represent a major health problem for patients having lymph node dissection [30,31]

Geppert et al. [31] compared peri-operative outcomes of patients having hysterectomy alone vs. hysterectomy plus sentinel nodes and hysterectomy plus full lymphadenectomy. They observed compared with hysterectomy alone, the additional average operative time for removal of sentinel lymph nodes was 33 minutes compared with 91 minutes for a full lymphadenectomy. The prevalence of leg lymphedema was significantly lower after sentinel node mapping in comparison to full lymphadenectomy (1.3% vs. 18.1%; $p<0.001$) [31]. Further randomized studies have to address the role of sentinel node mapping in reducing lymphatic complications in comparison to standard lymph node dissection.

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ONCOLOGIC OUTCOMES RELATED TO SENTINEL NODE MAPPING AND FULL LYMPHADENECTOMY

Accumulating evidence suggested that the adoption of sentinel node mapping have not impacted the outcomes in comparison to patients having full node dissection [28,32,33]. Several studies evaluated the accuracy of sentinel node biopsy in identify patients with lymphatic disease [34-37]. In fact, they evaluated how sentinel node mapping is effective in detect disease harboring in the lymph nodes considering patients having node mapping followed by full lymphadenectomy [34-37]. As aforementioned the FIRES trial reported sentinel node mapping sensitivity higher than 95% [28]. Recently, 2 comparative studies have been performed between 2 referral centers, the Mayo Clinic (Rochester, MN, USA) and the Memorial Sloan Kettering Cancer Centre (New York, NY, USA) [32,33]. These 2 centers performed two well-distinguished approaches in low risk EC patients (those with endometrioid histology and limited myometrial involvement). At Memorial Sloan Kettering Cancer Centre, a sentinel lymph node mapping algorithm was used per institutional protocol (this in presented above). At Mayo Clinic, full pelvic and para-aortic lymphadenectomy was performed in select cases deemed at risk for nodal metastasis (FIGO grade 3 and/or primary tumor diameter >2 cm). Details regarding these 2 approaches are presented elsewhere [32].

Data of more than 1,100 patients were collected and evaluated; 642 (57%) having sentinel node mapping and 493 (43%) having lymphadenectomy. Pelvic nodes were removed in 93% and 58% of patients, respectively ($p<0.001$); para-aortic nodes were removed in 14.5% and 50% of patients, respectively ($p<0.001$). Metastasis (including micrometastasis and isolated tumor cells) to pelvic nodes was detected in 5.1% and 2.6% of patients, respectively ($p=0.03$), and to para-aortic nodes in 0.8% and 1.0%, respectively ($p=0.75$). Survival outcomes were comparable with a 3-year disease-free survival rates were 94.9% (95% CI=92.4–97.5) and 96.8% (95% CI=95.2–98.5), respectively [32]. Two Italian institutions performed a similar comparison [34]. Overall, 802 patients were included. They observed that disease-free and overall survival was not influenced by type of nodal surgery (lymphadenectomy, sentinel node mapping followed by lymphadenectomy and sentinel node mapping alone) [34]. Interestingly, Buda et al. [34] corroborated data from, reporting a higher prevalence of positive nodes among patients having sentinel node mapping than in patients having conventional node dissection (patients with positive pelvic lymph nodes were 16.7% and 7.3%, in sentinel node mapping and lymphadenectomy groups, respectively; $p=0.002$) [34]. After a median follow-up shorter than 3 years, the authors reported no difference in recurrence and death rates among groups. However, the retrospective nature of these studies and the limited follow-up periods limit the value of these findings, thus making necessary further prospective evaluations.

The Mayo Clinic and Memorials Sloan Kettering Cancer Centre groups performed another study focusing on EC patients at high risk of nodal involvement (endometrioid histology [any grade], ≥50% myometrial invasion; serous or clear cell histology [any myometrial invasion]) [33]. Overall, 412 patients were included: 202 and 210 patients having sentinel node mapping and lymphadenectomy, respectively. In the intermediate-risk group, lymphatic disease was diagnosed in 35.4% vs. 28.0% of patients having sentinel node mapping and lymphadenectomy, respectively ($p=0.28$). In the high-risk group, lymphatic disease was diagnosed in 21.7% vs. 19.4% of patients having sentinel node mapping

and lymphadenectomy, respectively (p=0.68). Para-aortic lymph node assessment was performed significantly more often in intermediate-risk/high-risk groups in the lymphadenectomy cohort (p<0.001). In the intermediate-risk group, para-aortic nodal involvement was detected in 10.7% vs. 20.8% of patients having sentinel node mapping and lymphadenectomy, respectively (p=0.23). In the high-risk group, para-aortic nodal involvement was detected in 17.9% vs. 15.9% of patients having sentinel node mapping and lymphadenectomy, respectively (p=0.76) [33]. Data regarding disease-free and overall survival in these groups are pending.

The data of the literature suggested that sentinel node mapping is associated with similar oncologic outcomes than standard lymphadectomy. Additionally, patients undergoing sentinel node mapping might have a benefit from a more accurate detection of nodal metastases. In fact, sentinel node mapping increase our diagnostic ability to detect disease harboring in the lymph nodes in comparison to lymphadenectomy. Improving detection of extra-uterine disease might drive the choice to have adjuvant treatments, thus improving oncologic outcomes. Prospective data are warranted in order to confirm the impact of sentinel node mapping in the current management of EC.

PATHOLOGICAL ULTRASTAGING, MICROMETASTASIS AND ISOLATED TUMOR CELLS

Pathological ultrastaging is an integral part of the sentinel node mapping procedure. In fact, pathological protocols included that H&E and immohistochemical stains As described in breast cancer medical literature by the American Joint Committee on Cancer (AJCC), sentinel node mapping carrying the diagnosis of low volume disease: micrometastasis and isolated tumor cells [38]. Macrometastasis are defined by the presence of tumor cells in clusters greater than 2 mm; micrometastasis are microscopic clusters and single cells measuring >0.2 mm to ≤2 mm; isolated tumor cells are microscopic clusters and single cells measuring ≤0.2 mm. The presence of low volume lymphatic disease ranges from 25% to 63% across various studies on this issue [28,38-40]. The presence of low volume disease (micrometastasis and in particular isolated tumor cells) is of uncertain significance. In fact, no specific guidelines recommended the optimal management for patients with low volume lymphatic disease. Recently, Plante et al. [39] evaluated a series of 519 patients having sentinel node mapping among whom 85 were diagnosed with lymphatic disease. Macrometastasis, micrometastasis and isolated tumor cells were detected 43 (51%), 11 (13%) and 31 (36%) patients. Plante et al. [39] reported that 3-year progression-free survival of patients with isolated tumor cells (95.5%) was similar to what observed in node negative patients (87.6%) and patients with micrometastasis (85.5%), but it is statistically different in comparison to patients with macrometastasis (58.5%) [39]. The authors concluded that patients with isolated tumor cells should not have adjuvant treatment based on nodal status only, but the choice to have adjuvant treatments should be tailored to uterine factors (e.g., histology, myometrial invasion) [39]. However, we have to point out that difference in adjuvant treatments might influence results achieved by the authors, thus highlighting the needed of further prospective trials on this issue. Owing to the lack of mature data on the role of low-volume lymphatic disease, more evidence is needed. Further experiences are warranted in order to address the real impact of low volume lymphatic disease in EC patients.

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CONCLUSIONS

Sentinel node mapping represents an attractive mid-way between the omission of lymph node dissection and full lymphadenectomy. Accumulating evidence suggested that sentinel node mapping is safe and effective in EC patients. Thanks to the pathological ultrastaging, sentinel node mapping is able to identify more cases of lymphatic disease than conventional lymphadenectomy, thus improving our ability to tailor adjuvant treatments in high-risk patients. A large amount of data supported that sentinel node mapping is a safe and effective procedure; we have to overcome the concerns related to false negative rates since sentinel node mapping is characterized by a great diagnostic value. Paradoxically, sentinel node mapping might determinate overt treatments due to the detection of isolated tumor cells, that would not be detected during conventional staging procedures. Further long-term experiences are needed to better understand the beneficial effects and pitfalls related to the adoption of sentinel node mapping in EC patients. Personalized medicine and molecular characterization will represent the future in the management of EC patients.

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