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A critical assessment on the role of sentinel node mapping in endometrial cancer

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Endometrial cancer is the most common gynecologic malignancy in the developed countries. Although the high incidence of this occurrence no consensus, about the role of retroperitoneal staging, still exists. Growing evidence support the safety and efficacy of sentinel lymph node mapping. This technique is emerging as a new standard for endometrial cancer staging procedures. In the present paper, we discuss the role of sentinel lymph node mapping in endometrial cancer, highlighting the most controversies features.

Keywords: Endometrial Neoplasms; Hysteroscopic Injection; Lymph Node Excision; Sentinel Node

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries, with more than 54,000 new cases estimated for the year 2015 in the United States [1]. Surgery is the mainstay of treatment of EC. In particular, hysterectomy (with or without salpingo-oophorectomy) allows to remove primary tumor and to identify patients at high-risk of developing recurrences. However, no consensus on the execution of retroperitoneal staging still exists. The American College of Obstetricians and Gynecologists recommended the execution of lymphadenectomy, thus judging the execution of lymph node staging as an important part in EC treatment [2]. Similarly several retrospective studies evaluating the execution of lymphadenectomy suggested the prognostic and therapeutic role of retroperitoneal staging [3]. Notwithstanding, these results were not corroborated by the two randomized trials comparing hysterectomy plus lymphadenectomy vs. hysterectomy alone in the management of early stage EC [4]. In fact, they suggested that lymphadenectomy increases morbidity without improving oncologic outcomes. Albeit these two investigations were largely criticized due to the inherent biases of their study designs, they provide on overview of the lack of consensus on EC management [4].

Interestingly, in the last decades, the execution of sentinel lymph node mapping (SLNM) in EC staging has gained popularity among gynecologic oncologists. SLNM represents a half way treatment between the execution and the omission of node staging. Theoretically, SLNM upholds the effectiveness of standard lymphadenectomy allowing identifying node positive patients, minimizing the risk of developing lymphadenectomy-related morbidity in the whole EC population [5,6]; and in particular, in older and obese patients, who poorly tolerate adjunctive morbidity, and for whom the role of retroperitoneal staging remain controversial [7]. Additionally, several studies suggested the long-term effectiveness of this technique [5,6]. Recently, two large multi-institutional retrospective studies comparing SLNM versus systematic lymphadenectomy suggested the safety, feasibility, accuracy, and oncologic effectiveness of SLNM both in low- and high-risk EC [8,9].

However, three important features on the role of SLNM in EC deserve to be addressed. First, to date, two methods for sentinel node mapping are described: intracervical and subendo-

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metrial injection via hysteroscopy. Although the latter type is considered such as complex and time consuming technique (due to the need of hysteroscopic skills) it seems logical that a perilesional tracers injection provides a more reliable delineation of anatomic nodal distribution [9,10]. Cervical injection is effective in detecting lymphatic drainage of the uterus; while hysteroscopic injection is effective in detecting lymphatic drainage of the tumor. In fact, the uterus has complex lymphatic pathways: although the most common lymphatic drainage pathways are to iliac nodes, lesions located in the fundus may drain via the gonadal vessels to the high para-aortic area [11]. Hence, hysteroscopic injection may allow identifying patients with a disease harboring in the para-aortic nodes. This is paramount in patients with skip lesions (about 6% of all EC population) and node positive patients (characterized by a high rate of para-aortic node metastases; 60% and 70% for endometrioid and nonendometrioid EC, respectively) [3]. However, few investigations suggest that intracervical injection guarantees a more accurate node detection than hysteroscopic one [10]. In fact, the overall excellent detection rate related to cervical injection, the need for hysteroscopic skills and the longer learning curve of this procedure may be the main causes of this finding. Additionally, we have to point out that in low-risk patients, the potential effect of an accurate SLNM is diluted on the low proportion of patients with positive nodes (7% to 13%) [3,4]. In particular, growing evidence support that retroperitoneal staging procedures (including SLNM) can be safely omitted in low risk patients (characterized by The International Federation of Gynecology and Obstetrics [FIGO] grade 1 and 2 endometrioid EC located in the inner half of the myometrium and with tumor diameter less than 2 cm) [12-14]. Therefore, a very large sample size should be necessary to demonstrate a difference between the two techniques in term of detection of positive nodes and survival outcomes.

Second, in the last years different methods have been implemented for improving delineation of lymphatic drainage. Several studies suggested the applicability of radioactive technetium nano-colloid (^{99m}Tc) and methylene blue dye for SLNM [5,6,9]. However, ^{99m}Tc requires the use of nuclear medicine technology; while, methylene blue may correlate with surgical field contamination by the blue dye and a low detection rate. More recently, indocyanine green was introduced in order to overcome concerns of the use of the other tracers; in fact, accumulating evidence supports that indocyanine green upholds efficacy of other tracers, improving the identification of lymphatic ways [10]. Notwithstanding, further prospective studies are warranted in order to test efficacy of different tracers and possible cumulative effects in improving sentinel node detection rate.

Third, more importantly, the widespread SLNM will make a growing number of patients undergo just sentinel node removal, but not systemic lymphadenectomy. How patients with positive sentinel nodes have to be managed? Is a secondary surgical step useful? To date, no clear evidence on this issue is available. However, although it seems logical that the removal of metastatic nodes may correlate with improved survival no prospective data support this feature in the setting of EC patients. Lymphadenectomy represents a local/loco-regional treatment. Notwithstanding, the administration of adjuvant radiotherapy (administered even after systematic lymphadenectomy) has a role in sterilize metastatic sites, thus making unnecessary any secondary surgical efforts. Moreover, it is current evidence that lymphatic spread correlates with systemic dissemination and the presence of circulating tumor cells, suggesting the need for both systemic and loco-regional treatments in node positive EC [15]. Additionally, further studies aimed to weight the effects of the presence of isolated tumor cells, micro- and macro-metastases are necessary. In fact, owing to the implementation of ultrastaging during SLNM procedures, a growing number of patients will be diagnosed with isolated tumor cells and micro-metastases in comparison with patients undergoing conventional procedures.

In conclusion, the role of lymphadenectomy remains controversial. Albeit the therapeutic role of lymphadenectomy is still questioned its prognostic role is undoubted. Therefore, if we assume that lymphadenectomy have a pure diagnostic role, SLNM is enough to identify patients at high-risk of recurrence and to deliver target adjuvant treatments. SLNM provides important information to tailor adjuvant therapy and reduces lymphadenectomy-related morbidity and long-term sequelae of unnecessary adjuvant treatments. Further evidence on the role of SLNM in EC is warranted. Investigations have to focus to identify the best approach for tumor's lymphatic drainage (injection site and tracers type), thus reducing false negative rate and to indentify the best therapeutic adjuvant option for node positive EC. Owing to the relative low rate of lymphatic spread, multi-institutional collaborative studies are necessary in order to assess the efficacy and long-term oncologic effectiveness of SLNM, thus improving patients' care.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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