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Detection and feasibility of the SLN concept in the management of endometrial cancer. Literature review

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Abstract

Determining the lymph node status in endometrial cancer (EC) is essential for staging, prognosis and establishing the adjuvant therapy and is considered the most significant independent prognostic factor of recurrence. As the current imaging methods are not sufficient to stage EC patients, complete pelvic and para-aortic lymphadenectomies are being considered standard staging procedures. The introduction of the sentinel lymph node (SLN) concept in the management of EC can provide better staging information and is considered to be a valuable alternative to complete lymphadenectomy with a significant lower morbidity rates. The aim is to make a review of the current literature on the method of detection, and feasibility of the SLN concept in women with EC. A literature review was performed by searching for English articles in PubMed and Medline databases without date limitations. The keywords were: "endometrial cancer", "sentinel lymph node", "dissection", "lymphadenectomy". The use of the SLN biopsy can accurately stage intermediate-and high-risk women with stage 1EC, hence reducing unnecessary complete lymphadenectomies. Although SLN dissection continues to have encouraging results, because of the complex lymphatic drainage pattern of EC, many other issues need further clarification in order to implement the SLN concept in the standard management of early-stage EC.
Keywords: *endometrial cancer, sentinel lymph node, dissection, lymphadenectomy*

Introduction

Endometrial cancer (EC) is nowadays among the most frequent encountered gynecologic malignancies with an estimated incidence of 47130 cases in 2012 in the USA[(1)]. The majority of patients, between 85% and 91% are diagnosed in stage 1 with the most favorable prognosis, only 10% of patients with stage 1 EC being diagnoses with metastatic lymph nodes (LNs) compared to 20% of women with stages II and IIIA-B[(2)].

In spite of the criticism regarding the benefit of pelvic and paraaortic lymphadenectomy besides total hysterectomy and bilateral salpingooophorectomy as part of the surgical staging of EC[(3,4)], the only method in order to achieve an accurate staging of the disease is to perform a complete LN dissection which helps optimizing further treatments[(5)].

The presence of metastasis in the LNs represents the most important prognostic factors EC. In this regard, Morrow and coworkers[(6)] reported a the 5-year disease-free survival of 90% in patients without metastatic LNs compared to 75% in patients with metastatic pelvic LNs, and 38% with metastatic paraaortic LNs. Lurain et al.[(7)] reported an overall recurrence rate of 45% in women with positive pelvic LNs, 64% in women with positive paraaortic LNs compared to 8% in women with negative LNs. Patients with positive paraaortic LNS present a poorer prognosis compared to patients with positive pelvic LNs[(8)].

Taking into consideration the above presented results, it is clear that LN staging is primordial in order to establish the optimal therapeutic schema. Another study showed that patients with stage IB grade 3 who received lymphadenectomy had an improved 5-year disease-specific survival rate compared to low-risk patients in which no survival benefit has been observed[(9)]. Furthermore, the study conducted by Todo et al.[(10)] showed that patients undergoing pelvic and paraaortic lymphadenectomies have a better overall survival that patients submitted only to pelvic lymphadenectomy. However, women with pelvic LN dissection seem to have a higher risk of extrapelvic relapses compared to those who were submitted to paraaortic lymphadenectomy[(9)].

A pelvic and/or paraaortic lymphadenectomy has significant effects on postoperative evolution which made that the SLN concept to be introduced as a method to assess the node status of the patient.

SLN detection

In spite of the fact that it has not been validated as standard method of LN evaluation after examining the

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body literature we can conclude that there is increasing interest in SLN detection in early-stage EC[11,12]. The aim of the SLN concept is to identify the first node(s) in a regional lymphatic basin that receives lymph flow from the primary tumor. Therefore, when the SN is negative, a complete lymphadenectomy will be not performed, hence resulting in a lower rate of postoperative complications (e.g. lower extremity lymphedema, infected or symptomatic pelvic lymphocysts, chylous ascites)[13].

When it comes to the most accurate method of the SLN detection, it is debatable regarding of the method that provides the most reliable detection.

The rate of detection of SLNs depends on anatomic and technical factors, such as the adequacy of the injection, the site of injection, the substance injected, and the techniques used to identify the SLN[14]. The most used site of injections of blue dye and Tc-99m are: the uterine corpus subserosal/myometrial, the endometrium via hysteroscopy, and the cervix. The subserosal/myometrial injection has a detection rate which varies between 0% and 92%[15], the most highest detection rate for subserosal injection 92% being obtained by Altgassen and coworkers[16].

Although there is controversy whether the cervical injection of blue dye and Tc-99mm can adequately detect the SLNs in EC, studies have showed that cervical injection is the safe and is associated with a detection rate varying between 80% and 100%[17]. Futhermore, a deep cervical injection (corresponding to the paracervical and parametriallymphatics) with blue dye prior to total hysterectomy can adequately reflect the parauterine lymphatics, the area of uterine vessel drainage[18]. Abu-Rustum and colleagues[12] demonstrated that SLN mapping using cervical injection with combined Tc-99m and blue-dye in patients with grade 1 EC presents a detection rate of 86% and a sensitivity rate of 100%. It seems that women with grade 1 EC benefit the most from SLN biopsy as the tumor is confined to the uterus and is less likely to have the disruption of lymphatics that accompanies bulky disease that may impair the identification of SLNs.

The hysteroscopic injection represents another optimal method to highlight the complete lymphatic drainage of the uterus, but it is technically difficult to apply as well as difficult to accept from patients.

In recent studies conducted by How and colleagues[19] and Ballester et al.[20] the reported detection rate were 92% and 84% respectively, while the bilateral detection rate were lower, 72% and 69% respectively. The false negatives were 11% and 16%, respectively. The detection rates could be improved with the help of serial sections and immunohistochemistry which may contribute to the identification of intermediate and high risk patients.

Taking into consideration the false-negative rates and the unreliability of blue-dye injection alone, a peroperative algorithm has been implemented in order to obtain a better visualization of the SLNs, hence resulting in the omission of lymohadenectomy[21]. Barlin et al.[22] described the following steps: peritoneal and serosal evaluations and washings; retroperitoneal evaluation including excision of all mapped SLNs and suspicious nodes regardless of mapping; if there is no mapping on a hemipelvis, a side-specific pelvic, common iliac, and interiliac, lymphadenectomy was performed.

Lymphadenectomy versus SLN biopsy

The most important post-lymphadenectomy complication is the lower limb lymphedema. Paraaortic lymphadenectomy is doubles the risk of 30-day morbidity[23]. Ghezzi et al. reported a rate of lymphedema of 14% with no differences between laparoscopic and open surgery[24]. The reported risk factors of lower limb lymphedema are[25]: adjuvant radiation therapy, removal of the circumflex iliac LN distal to the external iliac LN, and resection of more than 31 nodes.

However, in spite of well-known complications that argue against the performance of lymphadenectomy, the reported overall rate of complication is low. For example, Querleu et al.[26] described a 2% rate of intraoperative complications with no associated lethality. About 71 symptomatic lymphocysts were observed and mostly managed by radiological drainage while 15% required surgery.

As mentioned above, the concept of SLN represents a promising alternative to complete lymphadenectomy as it is associated with a very low complication rate (e.g. infection at the injection site, bleeding). Moreover, the use of peroperative algorithm for risk determination could improve patient's staging with a reduction of lymphadenectomy-related morbidity.

However, the determination of the nodal status by pelvic and/or paraaortic lymphadenectomy still remains mandatory to optimally tailor adjuvant therapies and reduce local and distant recurrences[21].

When to perform SLN biopsy?

Besides the well-known risk factors such as: histological type, tumor grade, lympho-vascular space involvement, and depth of myometrial invasion, the Gynecologic Oncologic Group reported an overall incidence of LN metastases in clinical stage I EC of 3% in grade 1, 9% in grade 2 and 18% in grade 3. In stage IB, 20% of patients have LN metastases compared to less than 5% in stage IA[27].

The European Society for Medical Oncology subdivided early-stage EC patients into 3 risk categories for disease relapse and survival as follows[28]:

- low risk : stage IA, grade1 or 2,type 1 neoplasm;
- intermediate risk: stage IB, grade 1 or 2, type 1 neoplasm/stage IA, grade 3, type 1 neoplasm;
- high risk: stage IB, grade 3, type 1neoplasm/type 2 neoplasms.

Moreover, basing on the tumor size and the presence or absence of extension outside the uterus, Alhilli et al.[29] have defined the low-risk patients who have a very low risk of lymphatic dissemination or recurrence (<1%), and the intermediate- and high-risk patients who have a high

risk of 17% of LN metastasis and recurrence. Taking into consideration this classification, the study of Todo and coworkers[30] showed that low-risk patients have a risk of 3.3% of metastatic LNs, compared to 11.7% and 36.7% in intermediate-and high risk patients respectively. Therefore, it can be concluded that low-risk patients should not be supposed to lymphadenectomy while the SLN concept with or without lymphadenectomy should be applied in intermediate and high-risk patients.

Conclusions

Currently, an accurate surgical staging of EC is mandatory in order to obtain a proper evaluation of the lymphatic spread which has the most significant impact on prognosis and adjuvant therapy. As mentioned above, intermediate- and high risk patients should be submitted to SLN biopsy. By applying the above mentioned techniques for SLN detection, an accurate evaluation of the LNs is obtained with the lowest morbidity rate. Positive SLN(s) as well as a failed mapping are indications to perform pelvic and/or para-aortic lymphadenectomy.

However, because of the complex lymphatic drainage pattern of EC, the role of SLN biopsy is investigational as many issues such as the technique itself, the pathologic evaluation of the SLN, and the optimal treatment of patients with microscopic nodal disease, need further clarification. Larger studies are needed to establish the safety and accuracy of the SLN concept and the moment to implement it in the standard treatment of early-stage EC. ■

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