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RESEARCH ARTICLE

SENTINEL LYMPH NODE MAPPING FOR ENDOMETRIAL CANCER

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ABSTRACT

Endometrial cancer (EC) has an increasing incidence worldwide. Lymph node status is a strong predictive factor of recurrence. Therefore, determination of the nodal status is very important in order to optimally tailor adjuvant therapies and to reduce local and distant recurrences. Imaging modalities do not yet provide accurate lymph node staging, thus pelvic and aortic lymphadenectomies remain standard staging procedures. Sentinel lymph node (SLN) biopsy is intended to avoid extensive lymphadenectomy with its related morbidity and to provide significant oncologic information. This technique is emerging as a new standard for EC staging procedures.

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INTRODUCTION

Endometrial cancer (EC) is the most common malignancy of the female reproductive tract with an increasing incidence especially in developed countries. The majority of patients will present with clinically uterine-limited disease, but 10% would already have pelvic lymph node metastasis (LNM) despite favorable tumor characteristics (Creasman *et al.,* 2006). Also, 20% of the patients with EC extending outside of the uterus (stages II and IIIA-B) have LNM. The status of regional lymph nodes metastases is one of the most important prognostic indicators for overall survival (Mariani *et al.,* 2001), this aspect being best related by the fact that the new FIGO classification includes in different stages of the disease patients with positive pelvic and para-aortic lymph nodes respectively. The fact the FIGO stage at diagnosis is one of the most important prognostic factors for long term survival has been widely demonstrated. Most patients diagnosed in an early-stage of the disease report a good oncologic outcome with an overall survival for stage I ranging between 85–91% (Creasman *et al.,* 2006).

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The 5-year disease-free survival is 90% in cases without LNM, 75% in cases with pelvic LNM, and 38% with paraaortic LNM (Morrow *et al.,* 1991). Therefore, removal of pelvic and paraaortic LN has been recommended as part of a comprehensive surgical staging including total hysterectomy and bilateral salpingo-oophorectomy (1) (Creasman *et al.,* 2006). However, these results have remained controversial, two large randomized-control trials reporting that routine systematic lymph node dissection does not improve the long term prognosis in endometrial cancer; in consequence, the appropriate extent of lymph node dissection is still to be discussed, ranging from complete para-aortic and pelvic lymph node dissection to complete exclusion of lymph node dissection (Mariani *et al.,* 2008) The technique of sentinel lymph node mapping has been successfully implemented in patients with malignant melanoma, breast cancer and even cervical cancer. In patients with endometrial cancer this technique has been proposed in the last decades in order to reduce the risk of postoperative complications such as nerve damage, lymphedema and lymphocyst formation (Mariani *et al.,* 2008).

The extent of lymph node dissection: Even if isolated paraaortic involvement appears to be low (up to 6%), it occurs in approximately 50% of the patients with positive pelvic LN

and has an important prognostic value. Therefore, paraaortic area should be systematically part of the LN dissection (LND) (Mariani *et al.,* 2008). The SEPAL study demonstrated that systemic pelvic and para-aortic lymphadenectomy for patients in the high risk group were associated with increased overall and disease-free survival (Todo *et al.,* 2010). Abu-Rustum *et al.,* 2009, report that the risk of 'skip' metastases in case of negative pelvic SLN is about 2%. The number of lymph nodes to be removed for a reliable sampling is still not defined. The logistic regression model proposed by Chan *et al.,* 2007 demonstrated that resection of 21 to 25 nodes provided an 80% probability of detecting at least 1 positive lymph node. In the Mayo Clinic experience, Bakkum-Gamez *et al.,* 2011 considered a diagnostic LND as adequate if it retrieved at least 22 pelvic and 10 paraaortic LNs. Even if it constitutes a longstanding argument against LND, the rate of morbidity related to lymphadenectomy is relatively low, lower limb lymph edema remaining the most significant concern. Todo *et al.,* 2010 considered that adjuvant radiation therapy, removal of the circumflex iliac LN distal to the external iliac LN, and resection of more than 31 nodes were risk factors for the development of lower extremity lymph edema. The negative influence on the patient's quality of life emphasize the importance of careful patient selection for lymphadenectomy and underline the requirement of developing less invasive procedures as an alternative to standard LND.

Over the time, the management of EC has been heterogeneous across different institutions and countries, in particular regarding LN staging. Lymph node dissection (LND) is, to date, the only way to fully stage the disease and to determine patients that are likely to benefit from adjuvant therapy (Chan *et al.,* 2007; Bakkum-Gamez *et al.,* 2011; Seamon *et al.,* 2010). Despite the debate on prognostic and therapeutic relevance of LND in early-stage EC, most of the authors agree on stratifying patients into groups according to the risk of nodal involvement. Most of the risk factors for LNM include histological type, depth of myometrial invasion, lympho-vascular space involvement, and tumor grade. Endometrioid histology accounts for most cases (80%) and is graded from 1 to 3 sccording to the degree to which normal architecture is lost and the extent of nuclear atypia. The remaining cases (20%) consist of nonendometrioid histology- serous and clear cell histology, considered high grade with up to 50% lymph node metastases. Incidence of LNM in clinical stage I EC rises from 3% in grade 1 to 9% in grade 2 and 18% in grade 3. 20% of stage IB patients have LN metastases, compared to less than 5% of stage IA. The European Society for Medical Oncology (ESMO) subdivided early-stage EC patients into 3 risk categories for disease relapse and survival: (1) low risk: stage IA, grade 1 or 2, type 1 neoplasm; (2) intermediate risk: stage IB, grade 1 or 2, type 1 neoplasm/stage IA, grade 3, type 1 neoplasm; (3) high risk: stage IB, grade 3, type 1 neoplasm/type 2 neoplasms (Baekelandt *et al.,* 2009). Mariani *et al.,* 2008 identified a potential group of patients who were expected to have a low risk of nodal metastases and in which the morbidity of lymphadenectomy could be avoided. They defined these low-risk patients based on the combination of the intraoperative features: G1/G2 tumors, <50% myometrial invasion, <2 cm tumor diameter and no lymphovascular invasion (LVI).

Sentinel lymph node mapping

For patients with early stage disease, developing the best management plan involves a good balance between the risk of recurrence resulting from under treatment and the risk of complications from overtreatment. Sentinel lymph node (SLN) mapping attempts to accurately identify lymphatic drainage in order to select lymph nodes most likely to harbor disease, while also reducing the complications associated with lymphadenectomy. The SLN mapping is used when the EC is confirmed histologically and there is no evidence of extrapelvic metastases on initial imaging staging. Although the definition of the sentinel node was presented by Cabanas in 1977, the idea of the sentinel node had been described earlier by Braithwaite in 1923. The term 'the sentinel node' was first used by Gould *et al.,* in 1960. Dynamic development of the sentinel node biopsy technique began in 1992, when Morton *et al.* published their report on the use of this method in patients with skin melanoma. After the first report in 1999, the use of SLN mapping procedure in cervical cancer has also been examined in several studies (Echt *et al.,* 1999).

SLN mapping, might be an acceptable surgical strategy between extended lymphadenectomy and no lymphadenectomy in patients with endometrial cancer, minimizing the risk of developing lymphadenectomy-related morbidity; and in particular, in older and obese patients, who poorly tolerate adjunctive morbidity, and for whom the role of retroperitoneal staging remain controversial (Benedetti *et al.,* 2014). SLN mapping is based on the idea that lymph node metastases occur following lymph drains from the tumor. There is a spread of tumor cells to the first lymphatic station in SLN. This node should limit further distribution of tumor cells. If the SLN is negative than the nodes after SLN should also be negative (Kitchener *et al.,* 2009).Two large, randomized trials studying the role of systematic lymphadenectomy in patients with clinically early-stage EC report that the benefit of this procedure is limited to better surgical staging without an additional therapeutic effect (Kitchener *et al.,* 2009; Benedetti *et al.,* 2008). Therefore, the SLN concept has gained importance in EC as an accurate and reproducible technique in determining lymph node status. The false-negative rate of SLN technique has been shown to be low (Hauspy *et al.,* 2007). 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 (Eriksson *et al.,* 2015; Ducie *et al.,* 2015). Since incorporating the SLN mapping algorithm in 2008, the rate of complete lymphadenectomy has decreased from 65% to 23%. The median number of removed nodes decreased from 20 to 7 (Abu-Rustum, 2014).

Three methods of SLN mapping have been recommended: use of technetium-99, blue dye and indocyanine green (ICG). The radioactive tracer (^{99m}Tc) is injected into the cervix and is carried via lymph to SLNs. Gamma probes or single-photon emission computed tomography is used to detect the 'hot' nodes. Nejc D and Jeziorski A, 2008 have described lymphoscintigraphy, radiation dosage, and the problem of medical staff safety in surgery for breast cancer and skin melanoma. They analyzed the radiation dosage on the hands of

the surgeon, anesthesiologist, assistant surgeon, and nurses (Nejc *et al.,* 2006; Nejc and Jeziorsk, 2008). Blue dye (isosulfan blue 1, methylene blue 1%, patent blue 2.5% sodium) can be also injected, similarly to the radiotracer into the cervical submucosa and stroma, into 4 quadrants of the cervix. The complication rate is low; mostly allergic reactions (edema, pruritus, respiratory distress and shock) have been observed (Abu-Rustum, 2014). Fluorescent SLN imaging with green dye (indocyanine green - ICG) is the preferred mapping approach. The method of injection is similar to blue dye. Iodine allergy constitutes the main contraindication. According to the Memorial Sloan Kettering Cancer Center SLN algorithm, four milliliters (1.25mg/mL) of indocyanine green (ICG) is injected into the cervix divided into the 3- and 9-o'clock positions, with 1mL deep into the stroma and 1mL submucosally. Sentinel lymph nodes are examined with a protocol including both ultra staging with immunohistochemistry and 1-step nucleic acid amplification assay (Abu-Rustum *et al.,* 2009; Abu-Rustum, 2014; Siesto *et al.,* 2016).

SLN surgical algorithm includes peritoneal and serosal examination, retroperitoneal evaluation, including dissection of all SLNs and any suspicious nodes, and finally pelvic, common iliac and interiliac lymph node dissection, if there is no mapping on the pelvis (Abu-Rustum NR, 2014). After locating SLNs, each node is separately removed and analysed with frozen sections and in hematoxylin-eosin sections. Sentinel lymph nodes are considered positive if they contain macrometastases (tumor > 2 mm), micrometastases (tumor 0.2–2.0 mm), or isolated tumor cells (microscopic clusters and single cells measuring ≤ 0.2 mm), according to the American Joint Committee on Cancer (AJCC). Implementation of ultrastaging during SLNM procedures increases the number of patients diagnosed with isolated tumor cells and micro-metastases in comparison with patients undergoing conventional procedures (Bogani *et al.,* 2015). The false negative rate is defined as the number of procedures with negative SLN divided by the number of procedures in which SLN was recognized in the final microscopic examination of SLN or a positive lymph node was found in the removed iliac-obturator nodes (Favero *et al.,* 2015). One SLN mapping algorithm is offered by Cormier *et al.,* 2011, for cervical cancer to detect microscopic metastases. It is based upon a comprehensive study and according to them, all mapped SLN should first be studied with hematoxylin-eosin staining and considered for ultrastaging if negative inhematoxylin-eosin staining. Moreover, any suspicious node regardless of mapping should be excised and finally if there is no mapping on a hemipelvis, a side-specific lymph node dissection (including interiliac/subaortic nodes) should be performed. Based on the place of injection, two methods for SLNM are described: intracervical and subendometrial injection via hysteroscopy. Cervical injection is effective in detecting lymphatic drainage of the uterus; while hysteroscopic injection is effective in detecting lymphatic drainage of the tumor. The most common lymphatic drainage pathways are to iliac nodes, lesions located in the fundus may drain via the gonadal vessels to the high paraaortic area (Niikura *et al.,* 2013). Therefore, subendometrial injection may allow identifying disease harboring in these nodes. This is paramount in patients with skip lesions (about 6% of all EC). The main argument against the cervical injection is the lower para-aortic detection rate, but metastases are unlikely to be found in the para-aortic nodesin cases where pelvic nodes are negative (Abu-Rustum *et al.,* 2009)**.** Even if many studies suggest that intracervical injection provides a more accurate node detection than hysteroscopic one, the excellent detection rate related to cervical injection, the need for hysteroscopic skills and the longer learning curve of the procedure might influence this findings (Abu-Rustum *et al.,* 2008; Khoury-Collado and Abu-Rustum, 2008).

Many studies analyze cervical and hysteroscopic injections using blue dye and technetium-99 colloid, the detection rates being less than 80%. The use of fluorescence imaging after intracervical injection of indocyanine green (ICG) dye results in 87–100% detection rates and therefore appears superior to the use of blue dye or radioactive colloid (How *et al.,* 2015; Buda *et al.,* 2015). In 2011, Kang S *et al.,* performed a meta-analysis of 26 studies and reported that the use of pericervical injection was correlated with increased detection rate, while hysteroscopic injection was associated with lower detection rate. In more recent studies, the detection rates in SNLM were 92% (How *et al.,* 2015) and 88% (Ballester *et al.,* 2008). Bilateral detection rates were, however, much lower, 72% and 69%, respectively, and sensitivities were 89% and 84%. The false-negative rates in these studies were 11% and 16%, respectively. Lymph node staging can also be improved by the potential detection of micrometastases using ultrastaging protocols (serial section and immunohistochemistry). A recent French study (SENTI-ENDO) (Ballester *et al.,* 2011) describes an injection protocol in 133 patients who underwent sentinel lymph node biopsies, followed by complete lymphadenectomy. 90% of patients had at least one SLN detected. 17% of these had pelvic LN metastases. There were 3 patients with false-negative SLN, but all were type II high-grade cancers with greater than 50% invasion. SLN upstaged 10% of low-risk and 15% of intermediate-risk patients.

Conclusion

Even if sentinel lymph node mapping has not a routine use in clinical medicine, it has been acknowledged by the National Comprehensive Cancer Network guidelines as a viable option for the management of selected uterine malignancies. 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 endometrial cancer is needed. Investigations have to focus on identifying the best approach for tumor's lymphatic drainage (injection site and tracers type), reducing false negative rate. A multi-institutional randomized control trial is needed to assess the SLN mapping algorithm, SLN pathologic ultrastaging, and adjuvant treatment options for micrometastases and isolated tumor cells.

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