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Staging for endometrial cancer: The controversy around lymphadenectomy — Can this be resolved?

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Endometrial cancer remains the most common malignancy of the female genital tract. Lymph node metastasis is one of the most important prognostic factors, and stratification into pelvic lymph node invasion (stage IIIC1) and para-aortic lymph node invasion (stage IIIC2) improved the predictive value of the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification.

Radiological examination methods such as magnetic resonance imaging and positron emission tomography–computed tomography do not have good-enough sensitivity to avoid lymphadenectomy for the assessment of lymph node invasion. Prediction scores are becoming increasingly valuable to exclude lymph node metastasis in low-risk groups, and biomarkers could help to identify patients with high-risk lymph node metastatic probability. The therapeutic role of lymph node dissection remains a matter of debate. Several end points can be considered to evaluate the opportunity of lymphadenectomy in endometrial cancer.

First, we compare survival according to the realization, the extent, and the numbers of nodes removed during lymphadenectomy. Second, we assess the opportunity of lymphadenectomy in order

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to tailor adjuvant treatment modalities. Third, we analyze the surgical complication rate after pelvic lymphadenectomy.

Introduction

In Europe, endometrial cancer (EC) remains the third most common cancer diagnosed in 2012 [1]. Most cases occur in postmenopausal women. Based on histopathology, ECs are divided into two categories. Type I are typically low-grade adenocarcinomas that are usually estrogen related, are diagnosed early, and have a favorable prognosis. Type II ECs are not hormone dependent and are usually high-grade endometrioid adenocarcinomas, and papillary serous and clear cell carcinomas and carcinosarcomas [2].

Distant organ metastasis is the most important factor in determining patient survival in cancer. Metastasis is thought to occur through the blood vascular and lymphatic systems. Cancer cells are able to express growth factors and consequently have the capacity to create conduits for tumor metastasis. In EC, pelvic lymph nodes (LNs) are the most frequent location of metastasis. The major lymphatic trunks are the utero-ovarian (infundibulopelvic), parametrial, and presacral, which drain into the hypogastric, external iliac, common iliac, presacral, and para-aortic nodes [3]. Although a direct route of lymphatic spread from the corpus uteri to the para-aortic through the infundibulopelvic ligament has been suggested from anatomical and sentinel LN studies [4], direct metastases to the para-aortic LN are uncommon. This reflects the complexity of lymphatic drainage patterns of the uterus, particularly when compared to those observed in mapping studies of cutaneous or breast malignancies. At a larger scale, the underlying controversy around the clinical benefit of lymphadenectomy has not been solved. Here, we aim to summarize the main findings related to this commonly performed surgical staging procedure.

Prognostic value of LN metastasis

LN metastasis constitutes one of the most important prognostic factors of EC. In 1988, this information was included in the International Federation of Gynecology and Obstetrics (FIGO) classification. In 2009, the FIGO revised the classification of EC. Apart from merging FIGO 1988 stages IA and IB, LN invasion has been stratified into pelvic LN invasion (stage IIIC1) and para-aortic LN invasion (stage IIIC2). The prognostic performances of the 1988 and 2009 FIGO staging systems have been compared using the concordance indexes. The FIGO staging systems were not significantly different [5,6]. However, other studies have suggested that the 2009 FIGO staging system for EC is highly prognostic [7,8], particularly because stages IIIC1 and IIIC2 have different prognoses (5-year overall survivals are 57% and 49%, respectively [7])

An independent prognostic factor?

Primary pathological characteristics (myometrial invasion, cervical stromal invasion, histological type, lymphovascular space invasion (LVSI), and grade) are associated with the occurrence of LN metastasis. Consequently, we cannot exclude the negative impact of uterine risk factors associated with LN metastasis on survival independently of LN involvement [9–11]. To answer this question, Barrena Medel et al. compared the prognostic significance of uterine risk factor and nodal metastases and determined the independent effects on outcome [12]. Their results suggest that LN metastasis is an independent and the major prognostic factor, as survival in patients with LN metastasis and without uterine risk factors was worse when compared with patients without LN metastasis and with uterine risk factors.

Another approach to determining the prognostic impact of LN metastasis consists in building a score to predict survival in EC and in analyzing the impact of lymphadenectomy on the accuracy of this score. Such a score has been developed by Abu Rustum et al. [13] and been validated externally [14]. This score was designed to predict the 3-year survival probability, and it comprised the LN status. More precisely, the number of negative LNs was taken into account in this score as well as the 1988 FIGO stage, age at diagnosis, final FIGO grade, and histologic subtype. In this score, the LN status was