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Does the adoption of sentinel node mapping allow to design a new trial testing the value of retroperitoneal staging in endometrial cancer?

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Endometrial cancer is the most common gynecological malignancy in developed countries, accounting for about 63,000 newly diagnosed cases estimated in 2018, in the United States [1]. Population ageing, and the increase prevalence of obesity and diabetes are determining the increase in endometrial cancer incidence. Data from the United States cancer statistics suggested that incidence of endometrial cancer is increasing by more than 20,000 new cases per year in the last decade [2]. Despite the high prevalence of endometrial cancer, several features of its management remain unclear. In particular, the role of retroperitoneal staging [3]. In apparent early stage endometrial cancer, the execution of lymphadenectomy has undoubted important prognostic implications. Moreover, lymphadectomy might be useful to tailor adjuvant treatments in patients with disease harboring into the lymph nodes, thus having an indirect therapeutic value [4].

Several retrospective and prospective studies underlined the value of lymphadenectomy, but data of 2 large randomized trials focusing on the role of lymphadenectomy in endometrial cancer failed to observe beneficial effects of lymphadenectomy [5,6]. Benedetti Panici et al. [7], randomized patients with apparent International Federation of Gynecology and Obstetrics (FIGO) stage I endometrial carcinoma; these patients were randomly assigned to undergo pelvic systematic lymphadenectomy (n= 64) or no lymphadenectomy (n=250). The authors observed that pelvic lymphadenectomy improves surgical staging; patients in the lymphadenectomy arm are more likely to be diagnosed with stage IIIC than patients in the no-lymphadenectomy arm (13.3% vs. 3.2%; p<0.001). However, the execution of lymphadenectomy had no impact on survival outcomes [7]. Similarly, the ASTEC trial, observed that the execution of lymphadenectomy had no impact on survival outcomes. In this latter trial 1,408 women with histologically proven endometrial carcinoma, apparently confined to the uterine corpus, were randomly allocated to standard surgery (hysterectomy and bilateral salpingo-oophorectomy, peritoneal washings, and palpation of nodes; n=704) or standard surgery plus lymphadenectomy (n=704). After the adjustment for baseline characteristics and pathology details, the hazard ratio (HR) for recurrence-free survival was 1.25 (0.93–1.66; p=0.14) and overall survival was 1.04 (0.74–1.45; p=0.83). Pooled data of these 2 randomized trials confirmed that the execution of lymphadenectomy has not any therapeutic value, only to increase surgery-related complication rate [8]. However, several biases in the studies' design might impact on these results. These biases included: the inclusion of a large proportion of low-risk endometrial cancer, which might dilute the possible value of lymphadenectomy. In fact, owing to the low rate of nodal involvement in

low-risk endometrial cancer (about 10%–13%), it is not surprising that the 2 trials failed to find any therapeutic role for pelvic lymphadenectomy in the low-risk population. Second, no specific guidelines were available for postoperative adjuvant therapy. As aforementioned data on nodal status allow to tailor adjuvant treatment, thus decreasing unnecessary treatment in individuals at low risk of recurrence. However, in both study, adjuvant therapy administration rate was similar in lymphadenectomy and no-lymphadenectomy arms. Third, neither trial evaluated appropriately the role of paraaortic lymphadenectomy. In 2009, Todo et al. [9] designed a retrospective cohort study (the SEPAL study) aimed at assessing the role of paraaortic lymphadenectomy in endometrial cancer. In the SEPAL study, 671 patients at 2 tertiary centers in Japan were evaluated (325 had systematic pelvic lymphadenectomy and 346 had pelvic plus paraaortic lymphadenectomy) [9]. They observed that patient undergoing both pelvic and paraaortic lymphadenectomy experienced better overall survival than patients having pelvic lymphadenectomy alone. Moreover, an analysis of 328 patients with intermediate or high risk showed that independent patients' survival was improved with the execution of both pelvic and paraaortic lymphadenectomy (HR=0.48; 95% confidence interval [CI]=0.29–0.83; p=0.004). Additionally, they observed that adjuvant chemotherapy improved survival (HR=0.59; 95% CI=0.37–1.00; p=0.046) [9].

In the recent years, sentinel node mapping has emerged as a valid alternative method for nodal assessment. Several retrospective and prospective trials underlined the safety of lymph node mapping in endometrial cancer [10,11]. Prospective data underline that sentinel node mapping is safe and effective in detecting patients with disease harboring in the lymph nodes. Sentinel node mapping is related to a high sensitivity, specificity, and negative predictive value, that is reported to be 100% in some experiences [12-14]. The prevalence of false negative results is reported to negligible [10-14]. Interestingly, comparative studies aimed to test the non-inferiority of sentinel node mapping in comparison to standard lymphadenectomy showed that sentinel node mapping allows more precise identification of stage IIIC endometrial cancer patients. In fact, pathological ultrastaging, being an integral part of sentinel node mapping allows the detection of low volume disease. Low volume disease included the presence of micrometastasis and isolated tumor cells not detectable with conventional hematoxylin and eosin (H&E) pathological examination performed after full lymphadenectomy. According to the AJCC classification, micrometastasis and isolated tumor cells are classified as microscopic clusters and single neoplastic cells measuring >0.2 to ≤2 mm and as microscopic clusters and single neoplastic cells measuring ≤0.2 mm, respectively [11]. Several experience in the setting of sentinel node mapping underlined that the prevalence of low volume disease is high, being more than 50% of the whole group of stage IIIC patients. In 2013, Kim et al. [15], evaluated data of more than 600 endometrial cancer patients having sentinel node mapping. They observed that H&E examination detected 35 positive nodes (7%), while ultrastaging detected other 23 (4.5%) patients with stage IIIC disease, that otherwise would be missed. A growing number of retrospective investigations corroborated these data [15]. Focusing on prospective studies, we observed a surprisingly high prevalence of low volume disease detected thorough the adoption of sentinel node mapping. The SENTI-ENDO study is a prospective investigation reporting data of 133 patients were enrolled at nine centers in France. In this study at least 1 sentinel node was detected in 111 patients. Ultrastaging via immunohistochemistry and serial sectioning detected metastases undiagnosed by conventional histology in nine of 111 (8%) patients with detected SLNs, representing 9 of the 19 patients (47%) with metastases [12]. Similarly, other 2 prospective study showed that the adoption of sentinel node mapping provides a stage migration from stage I to III in a high proportion of endometrial cancer

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patients [12]. The FIRES trial reported that low volume disease in sentinel nodes (detected by ultrastaging) was 54% [13]; while the FILM trial reported low volume disease in 62% of positive nodes yielded [14]. In this latter study, 16 out of 176 patients (9%) had disease harboring in 21 sentinel lymph nodes. Macrometastatic disease was found in 8 (38%) of 21 sentinel nodes, micrometastatic disease in 5 (24%), and isolated tumor cells in 8 (38%) [14]. These prospective data strongly highlight that low volume disease is not uncommon in apparent early stage endometrial cancer. Therefore, owing to the increase of our ability to detect lymphatic spread in apparent early stage endometrial cancer we are calling to draw a new randomized trial evaluating the role of retroperitoneal staging (via sentinel node mapping) in endometrial cancer patients. Cumulative data from the ASTEC and the Italian trial published by Benedetti Panici et al. [7], suggested that in apparent early stage endometrial cancer undergoing lymphadenectomy the incidence of lymphatic disease is 9.3% (89 out of 950 patients) [8]. Considering power calculations adopted in other trials [7,8] and the fact that the adoption of sentinel node mapping would increase our ability to detect patients with a disease harboring in the lymph nodes of about 10%, we estimate that approximately 500 patients have to be randomized to demonstrate an improvement of 10% in 5-year overall survival, thanks to the adoption of sentinel node mapping. We are calling from a multi-institutional and an international collaborative effort in order to provide more insight in the value of nodal assessment in endometrial cancer. Considering the importance of this topic, a multi-institutional international protocol have to be designed. Furthermore, we have to identify precise guidelines for adjuvant therapy administration before treatment, thus reducing the possibility to obscure possible effects of nodal assessment.

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