Regarding: “Pathologic Ultrastaging Improves Micrometastasis Detection in Sentinel Lymph Nodes During Endometrial Cancer Staging”

To the Editor:

We read with great interest the article of Kim et al,¹ which highlights some important challenges of sentinel node (SN) mapping in early-stage endometrial cancer.

Taking a cue from the interesting article, we would like to add some aspects not covered in this valuable article, in particular the role of preoperative imaging using PET/CT and its possible integration in algorithm of SN mapping in women with high-risk early-stage endometrial cancer.

Data analysis from 508 women with endometrial cancer demonstrated that SN mapping with pathologic ultrastaging detects additional 4.5% of low-volume metastases that would otherwise go undetected with routine evaluations. The authors’ conclusion recommended the incorporation of pathologic ultrastaging SN in endometrial carcinoma with any degree of myoinvasion.

Regardless of those observations, some further questions arise as follows:

First question, “Is there really a commitment to offer lymphadenectomy to all women with preoperative early-stage high-risk endometrial cancer?”

If we take a look at what happens in breast cancer, it is reasonable to presume that the debate on whether or not performing lymphadenectomy in apparent early-stage endometrial cancer seems at least strange because data from 2 randomized trials and a meta-analysis, even if largely criticized for their flaws in design and conduction reducing the strength of their results, failed to demonstrate apparent therapeutic effects of systematic lymphadenectomy.

After the publication of the results of the Z0011, it showed no outcome difference in patients with positive SN between axillary dissection versus no further axillary surgery, raising doubts on the role of SN biopsy (SNB) itself. Based on these observations, a new prospective randomized trial comparing SNB versus observation when axillary ultrasound is negative in patients with small breast cancer, which are candidates for breast-conserving surgery, is ongoing at the European Institute of Oncology of Milan.²

In endometrial cancer, most recent clinical researches were focused on innovative imaging techniques for an accurate preoperative staging, as SN mapping and ¹⁸F-FDG PET/CT.

Looking to the subgroup of high-risk patients, 80% to 90% of women who undergo pelvic and/or aortic lymphadenectomy received a surgical overtreatment. These data should be considered in terms of morbidity and costs.

In intermediate and high-risk groups of the SEPAL study,³ results showed that the combination of pelvic and para-aortic lymphadenectomy can significantly improve survival in patients at intermediate and high-risk recurrence. However, the incidence of pelvic and para-aortic lymph node involvement was 14% and 18%, respectively, confirming that most women have little advantages from systematic aortic lymphadenectomy.

Furthemore, the issue regarding the risk of isolated aortic metastasis with negative pelvic node occurs in less than 1% of low-risk and 2% to 4% of high-risk endometrial cancer.

Second question, “Is there a workup algorithm or nomogram to assess the nodal risk involvement of high-risk cases with the aim to better select the percentage of women that can really benefit from retroperitoneal surgical staging or conversely are suitable only for SNB?”

Some argue that the rate of lymph node metastasis of randomized trial was most likely underestimated and that 15% of pelvic recurrence in node-negative patients seems to be related to the presence of occult micrometastases not detected by conventional hematoxylin and eosin pathologic assessment.

Considering that the risk of occult metastasis is independent of the baseline risk of nodal metastasis, the prognostic significance of micrometastases remains debatable.

Notwithstanding, in the article of Bendifallah et al,⁴ the authors suggested that primary tumor characteristics between patients with lymph node micrometastases and with macrometastases are significantly different. By applying a probability nomogram, they argue that the frequency of micrometastases seems to occur earlier and in tumors with lower oncological aggressiveness, suggesting that micrometastasis could represent an “intermediate state” between disease-free lymph node and macrometastasis. The same group in a recent study found that the prediction of lymph node micrometastasis detected by conventional histopathology seems to be feasible using a nomogram based on pathological characteristics of the hysterectomy specimen, whereas prediction of lymph node micrometastasis detected by ultrastaging on SN is not correlated with LN involvement probability. They finally suggest performing SN mapping in low and intermediate-risk endometrial cancers.

Looking at results published from Memorial Sloan-Kettering, the use of SN algorithms in preoperative stage I endometrial cancer reduces the need for standard lymphadenectomy without adversely affecting the rate of stage IIIC detection with an acceptable 5% false-negative rate.

Some Authors consider that the spatial resolution limit equal to or lower than 5 mm in the detection of micrometastases of ¹⁸F-FDG PET/CT cannot substitute a whole surgical staging.

Recently, Crivellaro et al⁵ presented a valuable assessment of the role of PET/CT in high-risk early-stage endometrial cancer, confirming our previous data on the use of PET/CT scan in preoperative risk assessment of pelvic nodal involvement of patients with endometrial cancer. In this group of patients, FDG PET/CT sensitivity, specificity, accuracy, and negative predictive value in detecting lymph node metastases were 78.6%, 98.4%, 94.7%, and 95.3%, respectively. Moreover, the maximal standardized uptake value, metabolic tumor volume, and total lesion glycolysis of the primary tumor are

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significantly correlated to lymph node metastases. Therefore, after the introduction in our clinical practice of SN mapping, we are still evaluating an innovative algorithm based on the integration of SNB and PET/CT scan to try to improve the detection rate of lymph node micrometastases in high-risk group of patients, defined as stage IB G2/G3 with endometrioid type and all stage with no endometrioid type (Fig. 1).

In high-risk early-stage endometrial cancer, we preoperatively stage patients with 18F-FDG PET/CT that allows to diagnose nodal macrometastases, greater than 5 mm, and also to exclude distant metastases. A systematic pelvic and aortic lymphadenectomy and SN mapping are then performed in case of positive imaging.

Conversely, either preoperative low-risk cases or high-risk subgroup with negative 18F-FDG PET/CT scan received only the SNB. Sentinel node biopsy with ultrastaging could be a trade-off between no nodal dissection and systematic lymphadenectomy.

Applying this algorithm, 37 women were staged both with 18F-FDG PET/CT and SN mapping (including pelvic + aortic radical lymphadenectomy). We discovered 6 cases with lymph node involvement, 3 of which with both 18F-FDG PET/CT and SN and 3 only by SN.

From our point of view, surgical staging of high-risk patients implemented dramatically because of the introduction of SN mapping. If applied in all patients, the algorithm will further minimize nodal-associated morbidity and allow reducing the need of a systematic pelvic and aortic lymphadenectomy in high-risk cases with negative PET/CT. Moreover, high-risk patients with negative PET/CT and women in low-risk group can be staged only by SN mapping.

Finally, waiting to better clarify with adequate time of follow-up, the prognostic significance of micrometastases, the application of dedicated algorithms also incorporating uterine risk factors of nodal metastasis (such as tumor size and location) is advisable to help physicians better select patients who are suitable for SN procedure and/or systematic lymphadenectomy, thus minimizing both retroperitoneal morbidity and the false-negative rate of SN mapping to further tailor and personalize the treatment of patients with apparent uterine-limited endometrial cancer.

**REFERENCES**


**Surgical Trocar Insertion Among Pregnant Patients**

*To the Editor:*

We have read your article by Vercellino et al with great interest. We agree that pelvic lymphadenectomy among pregnant patients with cervical cancer is a safe procedure that can improve patient’s prognosis. We would like to commend the authors for making such an extensive study involving pregnant patients with cervical cancer. However, we would like to make a suggestion regarding the methodology.

The authors mentioned that, “for patients less than 16 weeks (group16), the Palmer’s point was used as the camera trocar. A 10-mm umbilical trocar was used to take out the specimen and 2 accessory 5-mm trocars was placed on each side. They noted that in order to perform the lymphadenectomy on the contralateral side, the surgeon has to exchange places with the assistant. For patients more than 16 weeks (group24), 2 additional 10 mm trocars 2 cm above and below the umbilicus were used. In order to perform the lymphadenectomy on the contralateral side, the camera from the Palmer’s point was shifted to the 10 mm