Editorial

J Gynecol Oncol Vol. 23, No. 4:210-212
http://dx.doi.org/10.3802/jgo.2012.23.4.210

pISSN 2005-0380
eISSN 2005-0399

Journal of Gynecologic Oncology
jgo

Emerging concept of tailored lymphadenectomy in endometrial cancer

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Endometrial cancer is the most frequent cancer of female reproductive organs in western countries, and its incidence is steadily increasing in Japan. This type of tumor is generally regarded to be associated with relatively favorable prognosis because many patients have an early sign of genital bleeding that leads to early diagnosis. However, patients with lymph node metastasis are allocated to stage IIIC and have a 5-year survival rate of only ~50%. Endometrial cancer is a surgically staged disease, hence the diagnostic and prognostic significance of lymphadenectomy. In contrast, the therapeutic significance of lymphadenectomy has been a matter of debate for a long time. Treatment of endometrial cancer comprises local, regional and systemic control. Local control is achieved by removal of primary tumor by hysterectomy with sufficient surgical margins. Systemic control is achieved with systemic chemotherapy for clinical or occult hematogenous metastasis to distant organs. Regional control comprises eradication of cancer cells in regional lymph nodes, which is achieved by either lymphadenectomy or radiotherapy.

Two reports in *The Lancet* [1,2] strongly suggest that pelvic lymphadenectomy (PLX) has no therapeutic role in low-risk endometrial cancer, and complete pelvic and para-aortic lymphadenectomy (PLX+PALX) improves survival of patients with intermediate/high-risk endometrial cancer. The MRC ASTEC (A Study in the Treatment of Endometrial Cancer) trial [1] was a randomized controlled trial comparing standard treatment with total abdominal hysterectomy (TAH) plus bilateral salpingo-oophorectomy (BSO) and investigational treatment with TAH+BSO+PLX in early-stage endometrial cancer. PLX did not improve overall survival, and it is not recommended as a routine therapeutic procedure. In response to this recommendation, which contradicts the advice of some guidelines that do recommended PLX+PALX for patients with operable disease [2], Todo et al. [3] have reported the SEPAL (Survival Effect of Para-Aortic Lymphadenectomy) study, which is a retrospective cohort analysis of treatment of endometrial cancer in two tertiary center hospitals. One cohort was treated with PLX+PALX and the other with PLX alone, and the former improved survival of patients with surgically/pathologically defined intermediate/high-risk endometrial cancer. Notably, this survival effect was more significant in high-risk patients, 65% of whom had lymph node metastasis. In contrast, low-risk patients had no survival benefit from PLX+PALX, which suggests that lymphadenectomy itself has no survival benefit in surgically/pathologically determined low-risk endometrial cancer. It can be deduced from these two studies that lymphadenectomy does not have therapeutic effect in low-risk (low-risk of lymph node metastasis) endometrial cancer, and full lymphadenectomy for both pelvic and para-aortic areas has a therapeutic role in patients with intermediate/high-risk, especially node-positive, endometrial cancer.

In the post-ASTEC/SEPAL era, our discussion will be focused on tailoring lymphadenectomy in endometrial cancer in order to maximize the therapeutic effect of surgery and minimize its invasiveness and adverse effects. This will include: 1) preoperative assessment of the probability of lymph node metastasis in each patient to allocate only those with a certainty of lymph node metastasis to full lymphadenectomy; 2) standardization of type (PLX or PLX+PALX) and intensity (selective/sampling or systematic) of lymphadenectomy to optimize

Received Sep 6, 2012, **Accepted** Sep 6, 2012

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surgical therapy; 3) type of prospective study for validating usefulness of lymphadenectomy in patients with high risk of lymph node metastasis (randomized controlled trial or prospective comparative cohort study); and 4) identifying tumors with high potential of hematogenous systemic spread that are unlikely to benefit from formal lymphadenectomy. In this editorial, only the first point will be discussed in relation to an article by Kang et al. [4] in this issue. Diagnostic imaging using computed tomography, magnetic resonance imaging (MRI), and positron emission tomography are used for preoperative evaluation of lymph node metastasis. Positive predictive value is high, but sensitivity for detection of lymph node metastasis is not satisfactory [5-7]. Because of high positive predictive value, patients with positive diagnostic imaging should be candidates for formal lymphadenectomy. Among various histopathological factors, depth of myometrial invasion and tumor grade are well established risk factors for lymph node metastasis [8]. The former can be estimated preoperatively by MRI or intraoperatively by frozen section diagnosis or macroscopic evaluation. High-grade tumor, that is, G3 endometrioid or non-endometrioid tumor, can be diagnosed preoperatively by curettage and histopathological evaluation. The other predictive factor that is assessable in the preoperative settings includes serum CA-125 level [9,10]. Lymphovascular space invasion is a strong indicator of lymph node metastasis and patient survival. However, we do not have a reliable method to determine the presence and intensity of lymphovascular space invasion preoperatively or intraoperatively.

Patients with low probability of lymph node metastasis need not receive formal lymphadenectomy. Several investigators have proposed their own criteria for predicting lymph node metastasis, incorporating factors assessable in the preoperative setting [11-13]. The utility of these predicting or risk-scoring systems needs to be validated by large prospective studies. In such a circumstance, questions will be raised about what is a clinically acceptable cut-off value for accuracy of preoperative estimation of lymph node metastasis, which will be necessary in defining the endpoint of the validation study for the predicting system. In this issue of *J Gynecol Oncol*, Kang et al. [4] have tried to present a suggested false-negative rate as an index of the performance of a prediction model by analyzing three models for categorizing risk of lymph node metastasis by incorporating histopathological variables. They have proposed a false-negative rate <2% as an index of the usefulness of their prediction model, assuming that the prevalence of lymph node metastasis is 10% in the target patient cohort. This false-negative rate was obtained from postoperatively defined histopathological factors. Therefore, this value may not be directly applicable to preoperative predicting systems. However, their article provides us with the opportunity of discussing the index of reliability of a preoperative predicting system for lymph node metastasis in endometrial cancer. Acceptable false-negative rates for detecting lymph node metastasis using sentinel node biopsy are considered to be 5% for vulvar carcinoma [14] and 5% for breast cancer [15]. It would be acceptable to use those available predicting systems [11-13] in a prospective study to validate the survival effect of lymphadenectomy in order to exclude patients at low risk of lymph node metastasis.

CONFLICT OF INTEREST

No potential conflict of interests relevant to this manuscript was reported.

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