Editorial

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Preoperative selection of endometrial cancer patients at low risk for lymph node metastases: useful criteria for enrollment in clinical trials

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Important management concepts have emerged in the midst of the ongoing debate on the extent and therapeutic value of lymphadenectomy in endometrial cancer. Several groups have recognized that preoperative and intraoperative identification of low risk patient groups may allow the omission of lymphadenectomy thereby averting unnecessary morbidity and reducing costs while potentially achieving favorable oncologic outcomes [1-9]. Although the role of lymphadenectomy in endometrial cancer continues to be a topic of controversy, patients with low risk features (grade 1 or 2 histology, less than 50% myometrial invasion, endometrioid histology, tumor diameter ≤2 cm and absence of extrauterine disease) have been consistently shown to have a substantially low (<1%) risk of lymphatic dissemination [2,10,11]. Nevertheless, the aim of this editorial and the current paper is not to further deliberate the role of lymphadenectomy in endometrial cancer, but to describe preoperative risk stratification criteria that allow the identification of low-risk patients.

The authors of the current paper evaluate a population of 56 patients with low risk endometrial cancer who were surgically treated without lymphadenectomy (5 of which had lymphadenectomy based on intraoperative evaluation) [12]. These patients were preoperatively selected on the basis of their low lymph node metastasis risk score, which incorporates preoperative histologic grade, tumor volume (measured by magnetic resonance imaging [MRI]) and serum CA-125. Additionally MRI criteria for myometrial invasion and extrauterine disease were assessed and included in the decision to omit lymphadenectomy. The authors conclude that patients preoperatively selected on the basis of a lymph node metastasis score of 0 and absence of myometrial invasion or extrauterine disease by MRI have an excellent disease prognosis as demonstrated by the low risk of recurrence (1.8%) and 100% overall survival.

The authors build on their previous extensive experience with preoperative identification of low-risk endometrial cancer patients. They have previously shown that tumor volume, measured by MRI, serum CA-125 and preoperative tumor grade were independent risk factors for lymph node metastasis [6]. A similar study by the Korean Gynecologic Oncology Group recently showed that preoperative serum CA-125 in addition to deep myometrial invasion, lymph node metastasis, and extrauterine disease (both evaluated by MRI) identified low-risk patients for lymph node metastasis with high accuracy [8]. These criteria have been validated in two Japanese cohorts [13].

In the medical literature, data on the preoperative evaluation of the risk of lymph node metastases in endometrial cancer are limited. Imaging modalities *per se*, including computed tomography (CT), MRI, positron emission tomography (PET)/CT, are inadequate diagnostic tools for predicting lymph node status in patients with uterine malignancy [14]. However, when combined with other predictors (as in the present study), these imaging modalities may in fact aid in patient selection. For example, 40% to 50% of patients with positive nodes are found to have enlarged/suspicious lymph nodes on CT scan or MRI. Therefore, information on the size and characteristics of the lymph nodes may be helpful in having a more accurate estimate of the risk of lymph node metastases, in combination with other risk factors [15]. On the other hand, the sensitivity and specificity of CA-125 in the detection of

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pelvic lymph node metastases is approximately 72.4% and 75.1%, respectively, and 73.7% and 78.3% for paraaortic lymph node metastases, respectively [6]. Again, the lack of clear cut-off value and inconsistent correlation between serum CA-125 and lymph node metastases limit its clinical usefulness as an isolated predictive tool [16]. Intraoperative frozen section, on the other hand, has allowed for an individualized decision making approach to the selection of patients for lymphadenectomy at some institutions. The clinically relevant discordance rate between intraoperative frozen section and permanent pathology is as low as 1.7% when expertise in performing intraoperative frozen section is utilized [17,18]. Accuracy rates of intraoperative frozen section (agreement between frozen section and permanent section) of up to 97.8% have been described [18-22]. However, the lack of reliable frozen section at many institutions is a recognized limitation of selective lymphadenectomy based on intraoperative pathology findings. The use of preoperative biopsy results combined with intraoperative tumor diameter may mitigate some of the limitations of intraoperative frozen section. In the absence of extrauterine disease, and when tumor diameter ≤2 cm with International Federation of Gynecology and Obstetrics grade 1 or 2 endometrioid histology or complex and/or atypical hyperplasia on preoperative biopsy, the risk of lymph node metastasis or recurrence is estimated to be less than 1% and the 3-year recurrence free survival is 98.7% [7].

The current paper [12], when combined with the previous multiple reports from the same group [4,5,6], highlights the utility of a combination of preoperative selection criteria in the identification of patients at low risk for lymph node invasion through the use of preoperative biopsy, serum CA-125, and MRI. This is essential when the incorporation of preoperative selection criteria in upcoming clinical trials is to be considered. The development of an individualized surgical treatment algorithm is central to the management of endometrial cancer, given that approximately 27% of patients with endometrial cancer are deemed to be low risk based on intraoperative findings and may safely forgo lymphadenectomy, according to the Mayo Clinic criteria [2]. Strikingly similar results are observed in this paper [12], where the utilization of preoperative criteria allows for the selection of 27% of patients at low risk for lymph node invasion (1.8% positive lymph nodes) on the basis of preoperative grade/histology, serum CA-125, tumor volume and myometrial invasion by MRI.

In the present study [12], the authors demonstrate a high concordance rate (93.8%) between preoperative MRI and postoperative assessment of myometrial invasion. However, the limitations of preoperative MRI must be acknowledged. One possible concern is the reproducibility of the accuracy of preoperative MRI evaluation. In fact, estimates of deep myometrial invasion have been shown to have a sensitivity of 54% and specificity of 89%, and the overall diagnostic accuracy of myometrial invasion has been reported to range between 71% to 97% [23,24]. Additionally, determination of tumor volume and depth of invasion in patients with adenomyosis, intramural leiomyoma, thin atrophic endometrium, polypoid tumors as well as older patients with absent junctional zones on MRI is fraught with inaccuracy [24-26]. The use of MRI in the detection of depth of myometrial invasion is further associated with drawbacks related to cost and availability of resources and as such cannot be recommended for routine use in the preoperative evaluation of endometrial cancer. Serum HE4 is a promising ancillary test that may further modify preoperative selection criteria for lymphadenectomy. It has been shown that elevated serum HE4 correlates with myometrial invasion >50% and tumor diameter >2 cm and is more sensitive than CA-125 is identifying high risk patients [27].

The authors are to be congratulated for their efforts in addressing an important clinical question regarding the preoperative selection of patients at low risk for lymph node metastasis in endometrial cancer. Utilizing a combination of preoperative risk factors, the authors were able to identify low risk patients (27% of the population) which may safely forgo lymphadenectomy with excellent survival (though intraoperative frozen section was still utilized for performing lymphadenectomy in a few patients). Their approach with combining multiple risk factors is especially useful in patients enrolling in clinical trials, where accurate and predictive preoperative criteria are sought. However, until obvious cost issues are mitigated and a clear clinical benefit is demonstrated for the use of preoperative selection criteria for risk stratification, it is difficult to justify their use in routine clinical practice.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Dowdy SC, Borah BJ, Bakkum-Gamez JN, Kumar S, Weaver AL, McGree ME, et al. Factors predictive of postoperative morbidity and cost in patients with endometrial cancer. Obstet Gynecol 2012;120:1419-27.
2. Dowdy SC, Borah BJ, Bakkum-Gamez JN, Weaver AL, McGree ME, Haas LR, et al. Prospective assessment of survival, morbidity, and cost associated with lymphadenectomy in low-risk endometrial

cancer. Gynecol Oncol 2012;127:5-10.

3. Mariani A, Webb MJ, Keeney GL, Haddock MG, Calori G, Podratz KC. Low-risk corpus cancer: is lymphadenectomy or radiotherapy necessary? Am J Obstet Gynecol 2000;182:1506-19.

4. Todo Y, Watari H, Kang S, Sakuragi N. Tailoring lymphadenectomy according to the risk of lymph node metastasis in endometrial cancer. J Obstet Gynaecol Res 2014;40:317-21.

5. Todo Y, Okamoto K, Hayashi M, Minobe S, Nomura E, Hareyama H, et al. A validation study of a scoring system to estimate the risk of lymph node metastasis for patients with endometrial cancer for tailoring the indication of lymphadenectomy. Gynecol Oncol 2007;104:623-8.

6. Todo Y, Sakuragi N, Nishida R, Yamada T, Ebina Y, Yamamoto R, et al. Combined use of magnetic resonance imaging, CA 125 assay, histologic type, and histologic grade in the prediction of lymph node metastasis in endometrial carcinoma. Am J Obstet Gynecol 2003;188:1265-72.

7. AlHilli MM, Podratz KC, Dowdy SC, Bakkum-Gamez JN, Weaver AL, McGree ME, et al. Preoperative biopsy and intraoperative tumor diameter predict lymph node dissemination in endometrial cancer. Gynecol Oncol 2013;128:294-9.

8. Kang S, Kang WD, Chung HH, Jeong DH, Seo SS, Lee JM, et al. Preoperative identification of a low-risk group for lymph node metastasis in endometrial cancer: a Korean Gynecologic Oncology Group study. J Clin Oncol 2012;30:1329-34.

9. Akbayir O, Corbacioglu A, Goksedef BP, Numanoglu C, Akca A, Guraslan H, et al. The novel criteria for predicting pelvic lymph node metastasis in endometrioid adenocarcinoma of endometrium. Gynecol Oncol 2012;125:400-3.

10. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol 2008;109:11-8.

11. Java J, Walker J, Parker L, Metzinger D, Coleman R. Incidence of nodal metastasis in endometrioid endometrial cancer risk groups: a Gynecologic Oncology Group multicenter review. Gynecol Oncol 2011;120(Suppl 1):S4.

12. Mitamura T, Watari H, Todo Y, Kato T, Konno Y, Hosaka M, et al. Lymphadenectomy can be omitted for low-risk endometrial cancer based on preoperative assessments. J Gynecol Oncol 2014;25:301-5.

13. Kang S, Todo Y, Odagiri T, Mitamura T, Watari H, Kim JW, et al. A low-risk group for lymph node metastasis is accurately identified by Korean Gynecologic Oncology Group criteria in two Japanese cohorts with endometrial cancer. Gynecol Oncol 2013;129:33-7.

14. Pelikan HM, Trum JW, Bakers FC, Beets-Tan RG, Smits LJ, Kruitwagen RF. Diagnostic accuracy of preoperative tests for lymph node

status in endometrial cancer: a systematic review. Cancer Imaging 2013;13:314-22.

15. Ryo E, Yasugi T, Mizutani K, Kita T, Takeshita S, Ayabe T. Diagnostic usefulness of intraoperative ultrasonography in avoiding unnecessary para-aortic lymphadenectomy in women with endometrial carcinoma. Int J Gynecol Cancer 2011;21:859-63.

16. Dotters DJ. Preoperative CA 125 in endometrial cancer: is it useful? Am J Obstet Gynecol 2000;182:1328-34.

17. Kumar S, Medeiros F, Dowdy SC, Keeney GL, Bakkum-Gamez JN, Podratz KC, et al. A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. Gynecol Oncol 2012;127:525-31.

18. Ferreiro JA, Myers JL, Bostwick DG. Accuracy of frozen section diagnosis in surgical pathology: review of a 1-year experience with 24,880 cases at Mayo Clinic Rochester. Mayo Clin Proc 1995;70:1137-41.

19. Noumoff JS, Menzin A, Mikuta J, Lusk EJ, Morgan M, LiVolsi VA. The ability to evaluate prognostic variables on frozen section in hysterectomies performed for endometrial carcinoma. Gynecol Oncol 1991;42:202-8.

20. Kucera E, Kainz C, Reinthaller A, Sliutz G, Leodolter S, Kucera H, et al. Accuracy of intraoperative frozen-section diagnosis in stage I endometrial adenocarcinoma. Gynecol Obstet Invest 2000;49:62-6.

21. Convery PA, Cantrell LA, Di Santo N, Broadwater G, Modesitt SC, Secord AA, et al. Retrospective review of an intraoperative algorithm to predict lymph node metastasis in low-grade endometrial adenocarcinoma. Gynecol Oncol 2011;123:65-70.

22. Quinlivan JA, Petersen RW, Nicklin JL. Accuracy of frozen section for the operative management of endometrial cancer. BJOG 2001;108:798-803.

23. Hricak H, Rubinstein LV, Gherman GM, Karstaedt N. MR imaging evaluation of endometrial carcinoma: results of an NCI cooperative study. Radiology 1991;179:829-32.

24. Yamashita Y, Mizutani H, Torashima M, Takahashi M, Miyazaki K, Okamura H, et al. Assessment of myometrial invasion by endometrial carcinoma: transvaginal sonography vs contrast-enhanced MR imaging. AJR Am J Roentgenol 1993;161:595-9.

25. Scoutt LM, McCarthy SM, Flynn SD, Lange RC, Long F, Smith RC, et al. Clinical stage I endometrial carcinoma: pitfalls in preoperative assessment with MR imaging. Work in progress. Radiology 1995;194:567-72.

26. Demas BE, Hricak H, Jaffe RB. Uterine MR imaging: effects of hormonal stimulation. Radiology 1986;159:123-6.

27. Kalogera E, Scholler N, Powless C, Weaver A, Drapkin R, Li J, et al. Correlation of serum HE4 with tumor size and myometrial invasion in endometrial cancer. Gynecol Oncol 2012;124:270-5.

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