



Editorial

Enough already: Is this the end of comprehensive lymphadenectomy in endometrial cancer or are further trials needed?



Lymph node metastasis is indisputably considered one of the most important prognostic factors in endometrial cancer (EC) [1]. While hysterectomy and comprehensive staging with pelvic and aortic lymphadenectomy are considered the surgical gold standard, only 7–15% of all patients with apparent early-stage disease will actually harbor lymphatic metastases. The risks of systematic lymphadenectomy in this setting are well established, and include hemorrhage, nerve injury, lymphedema, lymphocyst, greater time under anesthesia, and a higher cost of cancer care [2]. Given these potential hazards and that lymphatic spread occurs in only a handful of women with EC at disease presentation, subjecting 100% of patients to systematic lymphadenectomy would be potentially overtreating nearly all of them.

Surgical staging in endometrial cancer has undergone a fairly radical evolution in the last three decades. Prior to the 1980s, a systematic pelvic and aortic lymph node dissection was not performed. However, in 1987, the landmark GOG 33 trial was published describing the increased risk of lymphatic metastases, especially pelvic, in those with deep myoinvasion or higher-grade EC tumors [1]. An emphasis on “complete” lymphadenectomy (systematic pelvic and aortic dissection) was considered to be reasonable, and possibly therapeutic. In the early 2000s, an effort to better define those patients who would most benefit from surgical staging was undertaken by Mariani and colleagues at the Mayo Clinic [3]. In a retrospective analysis, the investigators observed that tumors with grade 1 or 2 histology, ≤ 2 cm in diameter, and $\leq 50\%$ myometrial invasion had a lymph node metastasis rate of virtually zero—thus rendering the risks of lymphadenectomy in these patients greater than the benefits. Notably, for patients not meeting these “Mayo” criteria, it was recommended to continue with the established surgical paradigm, including systematic lymphadenectomy with extended dissection up to the renal vessels. This was followed by two landmark European Phase III studies which found no survival benefit to performing routine surgical staging in early-stage endometrial cancer, although both studies have been criticized for including a large number of patients at low risk of lymphatic metastasis, and therefore, lacking power to detect a survival difference in those at greatest risk of lymphatic dissemination [4,5]. Contrary to these findings, the large, retrospective SEPAL study from Japan showed that in those patients at intermediate or high risk of lymphatic metastasis, that systematic pelvic and aortic lymphadenectomy was independently associated with overall survival [6].

By 2010, there was a growing movement away from performance of systematic lymphadenectomy in all women with EC and an effort to simplify, or tailor, the staging to patients at most risk for lymphatic spread. Led by Abu Rustum and colleagues at Memorial Sloan Kettering Cancer Center (MSKCC), the dawn of the

sentinel lymph node (SLN) era in EC was transformative and ushered in an era of “less is more” in EC surgical staging [7]. Several retrospective and a handful of prospective cohort studies have reported on the safety, feasibility, and accuracy of SLN mapping in this disease, with an overall sensitivity of 97–100%, and a pooled negative predictive value of 99.7% [7–9]. The FIRES trial (a prospective, cohort of study of 385 patients with clinical stage I EC of all histologies and grades who underwent robotic-assisted hysterectomy and SLN mapping with indocyanine green dye followed by systematic lymphadenectomy) also demonstrated excellent sensitivity (97.2%) and negative predictive value (99.6%) with the SLN technique [10]. In addition, SLN mapping appeared to increase the rate of positive nodal detection through the use of ultra-staging techniques, and demonstrated utility in women with both low and high grade tumors [7,10,11]. Further, two systematic reviews and meta-analyses conducted at Johns Hopkins Hospital and the Fondazione IRCCS Istituto Nazionale dei Tumori de Milano, respectively, concluded that this technique is accurate, sensitive, and does not appear to be associated with worse oncologic outcomes compared to systematic lymphadenectomy [8,9]. Based on these data, fairly widespread adoption of SLN mapping in EC by gynecologic oncologists occurred. Despite the need for specialized equipment, a recent survey of SGO members suggested that this technique has been widely adopted with 80% of respondents indicating they use SLN mapping for endometrial cancer [12]. However, the survey had a 20% response rate, increasing the chance these results were biased by an enthusiastic minority of surgeons.

In this issue of *Gynecologic Oncology*, the expert Mayo Clinic and MSKCC research teams have teamed up to study an additional question related to SLN utility in EC. Multinu et al. report on their retrospective comparison of two institutional cohorts: a historical patient group (2004–2008) from the Mayo Clinic in which all women with apparent early-stage EC were staged with systematic lymphadenectomy (LND), and a somewhat more contemporary and similar patient cohort (2006–2013) from MSKCC in which women were staged using the institutional SLN mapping algorithm [13]. The study focus was on patients who had non-bulky (i.e. microscopic), metastatic lymphatic disease identified on pathologic staging. Notably, the study authors excluded any patients with imaging findings concerning for metastatic disease and any cases of nodes with isolated tumor cells identified. There were 104 patients with positive nodes (6.7% of the total study population), 48 in the LND cohort and 56 in the SLN cohort. A parsimonious multivariable model was used to examine factors independently associated with recurrence and survival. The authors reported no significant differences in disease-specific survival between the two groups, and on multivariable analysis, noted better progression-free

survival outcomes for patients treated with combination chemotherapy and radiotherapy compared to either modality alone. They concluded that “in patients with non-bulky, Stage IIIC EC who receive combined chemotherapy and radiotherapy, systematic lymphadenectomy could be omitted without compromising oncologic outcomes.”

This novel analysis is one of the first to address survival outcomes in women with positive, non-bulky SLNs and is an important addition to literature authored by experienced and respected investigators. It suggests that in women treated with contemporary, multimodal adjuvant therapy, that a more limited lymph node assessment strategy is reasonable. We congratulate the authors for their continued important contributions to the field. While provocative and hypothesis generating, the study has a few limitations: 1) The retrospective analysis was not powered to examine differences in survival or to derive conclusions regarding best adjuvant treatment strategies; 2) The two lymph node assessment groups differed significantly in important ways (e.g., the LND cohort was more likely to be treated by laparotomy, was heavier, had lower rates of tumoral lymphovascular space invasion, had more total lymph nodes removed (as expected), and higher rates of positive aortic nodes); 3) Given the temporal difference in treatment between the two cohorts, the authors censored follow-up data at 5 years; 4) Recurrence and survival outcomes in EC are known to be heavily influenced by use of adjuvant therapy, and there were significant differences noted between the cohorts, including more women who received chemotherapy ± brachytherapy in the SLN cohort; 5) The positive nodal rate of 6.7% seems low for the overall cohort, given that the FIRES trial reported a 12% positive nodal rate and included a greater number of low risk patients; and 6) The use of a parsimonious multivariate model may have “fit” the data best compared to other models in this case, but the modelling approach requires fewer parameters than other multivariate models and thus may not account for a sufficient number of confounding factors. Finally, given the significant differences in demographic, clinical and adjuvant treatments between the two cohorts, the use of a propensity-matched analysis may have been considered to study this question. In the end, however, these data add to the circumstantial evidence supporting SLN mapping as an alternative surgical management in EC.

SLN mapping may provide our patients with the right balance of critical pathologic information and acceptable perioperative risks. For some, the compelling accumulating evidence in EC has been sufficient to change their clinical practice, and many may believe “enough already” with systematic, or complete, lymphadenectomy in this setting. Certainly, the National Comprehensive Cancer Network Uterine Cancer Guidelines and the Society of Gynecologic Oncology both recognize SLN mapping as an acceptable alternative standard approach to lymphatic assessment [14,15]. Importantly, however, both organizations note the absence of randomized data to inform these recommendations. SLN mapping is the standard in the management of several other cancers which metastasize primarily through the lymph nodes, including breast cancer and melanoma, and outcomes in these settings were validated through randomized controlled trials. While acknowledging the many differences between these cancers and EC, as well as the great challenges and costs associated with performing randomized surgical studies, a Phase III clinical trial comparing SLN mapping to systematic lymphadenectomy could potentially confirm once and for all the compelling findings of the current study and the many SLN cohort studies that have come before. If we have learned anything from the recent LACC trial in cervical cancer [16], it is ideal to validate retrospective and prospective surgical cohort studies in a randomized fashion. A trial with a focus on higher grade tumors may be higher yield, since two randomized studies have already established the lack of utility for surgical staging in women with low

grade, low risk tumors. Such a trial will require thousands of patients and international cooperation. It will be worth the effort.

Disclosures

Drs Ferriss and Fader have nothing to disclose.

Contributions

Both authors participated in the conception, writing, critical review, and approval of the final manuscript.

References

- [1] W.T. Creasman, C.P. Morrow, B.N. Bundy, H.D. Homesley, J.E. Graham, P.B. Heller, Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study, *Cancer* 60 (1987) 2035–2041.
- [2] Y. Todo, R. Yamamoto, S. Minobe, Y. Suzuki, U. Takeshi, M. Nakatani, et al., Risk factors for postoperative lower-extremity lymphedema in endometrial cancer survivors who had treatment including lymphadenectomy, *Gynecol. Oncol.* 119 (1) (2010) 60–64.
- [3] A. Mariani, S.C. Dowdy, W.A. Cliby, B.S. Gostout, M.B. Jones, T.O. Wilson, et al., Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging, *Gynecol. Oncol.* 109 (1) (2008) 11–18.
- [4] P. Benedetti Panici, S. Basile, F. Maneschi, A. Alberto Lissoni, M. Signorelli, G. Scambia, et al., Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial, *J. Natl. Cancer Inst.* 100 (23) (2008) 1707–1716.
- [5] H. Kitchener, A.M. Swart, Q. Qian, C. Amos, M.K. Parmar, Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study, *Lancet* 373 (9658) (2009) 125–136.
- [6] Y. Todo, H. Kato, M. Kaneuchi, H. Watari, M. Takeda, N. Sakuragi, Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis, *Lancet* 375 (9721) (2010) 1165–1172.
- [7] N.R. Abu-Rustum, F. Khoury-Collado, N. Pandit-Taskar, R.A. Soslow, F. Dao, Y. Sonoda, et al., Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? *Gynecol. Oncol.* 113 (2) (2009) 163–169.
- [8] A.J. Bodurtha Smith, A.N. Fader, E.J. Tanner, Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis, *Am. J. Obstet. Gynecol.* 216 (5) (2017) 459–476, e10.
- [9] G. Bogani, F. Murgia, A. Ditto, F. Raspagliesi, Sentinel node mapping vs. lymphadenectomy in endometrial cancer: a systematic review and meta-analysis, *Gynecol. Oncol.* 153 (3) (2019) 676–683.
- [10] E.C. Rossi, L.D. Kowalski, J. Scalici, L. Cantrell, K. Schuler, R.K. Hanna, et al., A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study, *Lancet Oncol.* 18 (3) (2017) 384–392.
- [11] P.T. Soliman, S.N. Westin, S. Dioun, C.C. Sun, E. Euscher, M.F. Munsell, et al., A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer, *Gynecol. Oncol.* 146 (2) (2017) 234–239.
- [12] M. Renz, E. Diver, D. English, E. Kidd, O. Dorigo, A. Karam, Sentinel lymph node biopsies in endometrial cancer: practice patterns among gynecologic oncologists in the United States, *J. Minim. Invasive Gynecol.* (2019).
- [13] F. Multinu, J. Ducie, A.G.Z. Eriksson, B.A. Schlappe, W.A. Cliby, G.E. Glaser, et al., Role of lymphadenectomy in endometrial cancer with nonbulky lymph node metastasis: comparison of comprehensive surgical staging and sentinel lymph node algorithm, *Gynecol. Oncol.* 155 (2) (2019) 177–185.
- [14] W.J. Koh, N.R. Abu-Rustum, S. Bean, K. Bradley, S.M. Campos, K.R. Cho, et al., Uterine neoplasms, version 1.2018, NCCN clinical practice Guidelines in oncology, *J. Natl. Compr. Cancer Netw.* 16 (2) (2018) 170–199.
- [15] R.W. Holloway, N.R. Abu-Rustum, F.J. Backes, J.F. Boggess, W.H. Gotlieb, W. Jeffrey Lowery, et al., Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations, *Gynecol. Oncol.* 146 (2) (2017) 405–415.
- [16] P.T. Ramirez, A. Obermair, Minimally invasive or abdominal radical hysterectomy for cervical cancer, *Reply. N Engl J Med.* 380 (8) (2019) 794–795.

James Stuart Ferriss, Amanda N. Fader*

The Kelly Gynecologic Oncology Service, Johns Hopkins University School of Medicine, Baltimore, MD, USA

* Corresponding author.

E-mail address: afader1@jhmi.edu (A.N. Fader).