

Does surgical treatment of atypical endometrial hyperplasia require referral to a gynecologic oncologist?



David I. Shalowitz, MD, MSHP; Alexandra Goodwin, BS; Nicholas Schoenbachler, MD

Patients with atypical endometrial hyperplasia in the United States are commonly referred to a gynecologic oncologist, given a moderate risk of concurrent carcinoma. However, selective referral of patients to nononcologic gynecologic surgeons for surgical treatment of atypical endometrial hyperplasia may offer increased access to care without compromising clinical outcomes. Nononcologic surgeons who consider providing surgical treatment for atypical endometrial hyperplasia must be able to offer minimally invasive surgery when appropriate and have sufficient surgical volume to deliver optimal clinical outcomes. Patients considering referral to a nononcologic surgeon must be thoroughly counseled regarding the risk of occult malignancy, the possibility of a second surgery for lymph node evaluation and/or oophorectomy, and the risk of morbidity that may accompany a second surgery. Available data suggest that approximately 2–6% of patients will have postoperative risk factors meriting consideration of a second surgery. Patients who are high-risk surgical candidates or who may desire nonsurgical or fertility-sparing treatment should universally be referred for consultation with a gynecologic oncologist.

Key words: atypical endometrial hyperplasia, cancer care delivery research, fertility-sparing treatment, gynecologic oncology, minimally invasive surgery

Atypical endometrial hyperplasia (AEH), also called endometrial intraepithelial neoplasia, is an uncommon finding on endometrial biopsy with an estimated incidence of 17 cases per 100,000 women per year.^{1,2} While AEH is itself a premalignant lesion, a meta-analysis of 2550 cases across 31 studies suggested that 38% of patients who have a pre hysterectomy endometrial biopsy

consistent with AEH will have concurrent endometrial carcinoma on final pathology.³

For appropriately selected patients who do not desire fertility preservation, definitive surgical treatment of AEH entails total hysterectomy with bilateral salpingectomy with or without oophorectomy, depending on patients' age and menopausal status. While routine comprehensive pelvic and paraaortic lymphadenectomy is unnecessarily morbid for these patients,⁴ given the possibility of concurrent carcinoma, surgical treatment may ideally also include either triage to lymphadenectomy by intraoperative pathologic evaluation of the uterus⁵ or routine sentinel lymph node biopsy.⁶

Referral to a gynecologic oncologist for AEH appears to be commonplace in the United States. In one recent, large sample, 67% of patients with AEH on postoperative pathology had undergone hysterectomy with a gynecologic oncologist⁷; however, this is likely a significant

underestimate of patients with AEH on the initial biopsy prompting surgery.

Commentators from the United States have advocated that all cases of AEH be referred for evaluation and treatment by a gynecologic oncologist,^{6,8} owing to the specialized surgical skill required for staging lymphadenectomy as well as the superior clinical outcomes experienced by women with uterine cancers who are treated by oncologic surgeons.⁹ However, the American College of Obstetricians and Gynecologists and the Society of Gynecologic Oncology do not provide specific, official guidance on whether evaluation and surgical treatment of AEH requires a gynecologic oncologist.^{4,10}

In contrast, the guidelines for the management of endometrial hyperplasia of the Royal College of Obstetricians and Gynaecologists suggest that referral to a gynecologic oncologist is necessary only when medical or fertility-sparing treatment is pursued.¹¹ Likewise, while the Society of Obstetricians and Gynaecologists of Canada also does not comment specifically on surgical triage of AEH, Cancer Care Ontario, the government of Ontario's principal advisory body on cancer, classifies referral to a gynecologic oncologist for presumed low-grade endometrial carcinoma as optional.¹²

Because there is minimal specific guidance on this issue and a clear diversity of opinion, in this article we explore the implications of universal vs selective referral of patients with AEH to gynecologic oncologists for surgical management. Our discussion is oriented toward clinical practice in the United States because we anticipate that individual clinicians' decisions to adopt universal or selective referral for surgery will depend on specific practice pattern, patient population, and availability of subspecialty resources.

We also hope that this discussion will aid in the creation of policies for referral

From the Departments of Obstetrics and Gynecology (Dr Schoenbachler) and Implementation Science (Dr Shalowitz), School of Medicine (Ms Goodwin), and Section on Gynecologic Oncology, Department of Obstetrics and Gynecology (Dr Shalowitz), Wake Forest School of Medicine, Winston-Salem, NC.

Received Oct. 12, 2018; revised Dec. 1, 2018; accepted Dec. 3, 2018.

The authors report no conflict of interest.

Corresponding author: David I. Shalowitz, MD, MSHP. dshalowi@wakehealth.edu

0002-9378/\$36.00

© 2018 Elsevier Inc. All rights reserved.

<https://doi.org/10.1016/j.ajog.2018.12.010>

at the health system, regional, and national levels. Importantly, we reinforce that women with AEH who may desire fertility-sparing or nonsurgical management or who may not be surgical candidates should universally be referred to a gynecologic oncologist for consultation; there is substantial agreement on this point internationally.

Two pathways

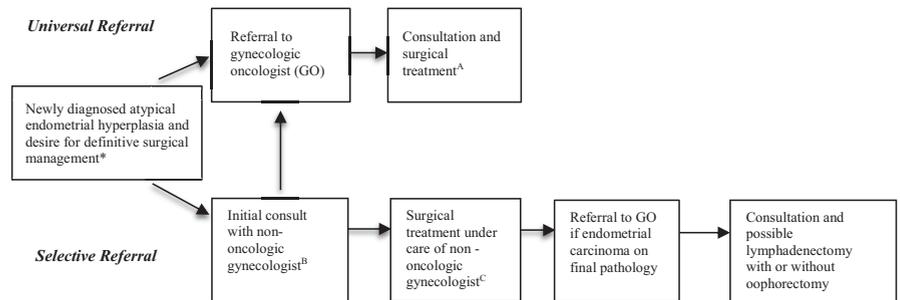
We consider 2 approaches to triage of patients with a new diagnosis of AEH (Figure). Under the first pathway (universal referral), patients with AEH on endometrial biopsy are uniformly referred to a gynecologic oncologist for consultation, surgical treatment, and follow-up as needed. Under the second (selective referral), initial surgery need not be performed by a gynecologic oncologist. However, patients who after counseling prefer surgery with a gynecologic oncologist are referred for subspecialty care.

Additionally, all patients with endometrial cancer on final surgical pathology are referred for a gynecologic oncology consultation. Referral sources under either pathway may include primary care physicians and nonphysician providers as well as obstetrician-gynecologists.

Importantly, both pathways presume that surgeons considering initial surgical treatment of AEH should have sufficient surgical volume to offer women undergoing hysterectomy optimal clinical outcomes¹³ as well as to offer minimally invasive laparoscopic¹⁴ or vaginal hysterectomy¹⁵ as appropriate. Furthermore, surgery should take place in a setting with resources to manage potential perioperative complications (Table).¹⁶

If any of these conditions is not met or if there is concern over medical or surgical aspects of the patient's perioperative care, expert consultation should be obtained. In some centers, general gynecologists may opt to pursue surgery for AEH jointly with a gynecologic oncologist. However, we anticipate that this approach, while reasonable, is available in only a small minority of settings and is not considered further here.

FIGURE
Referral pathways



^A Total hysterectomy with bilateral salpingectomy, lymph node evaluation, with or without oophorectomy

^B Patients who, after discussion, prefer surgery with a gynecologic oncologist are referred for subspecialty care

^C Total hysterectomy with bilateral salpingectomy with or without oophorectomy

*Patients who desire fertility preservation or medical management, or who may not be surgical candidates should be referred to a gynecologic oncologist.

Shalowitz. Surgical treatment and referral for atypical endometrial hyperplasia. *Am J Obstet Gynecol* 2019.

Surgical considerations

Under a policy of universal referral, all patients with AEH would undergo hysterectomy by a gynecologic oncologist. If safe and technically feasible, all these patients should be evaluated for lymph node metastases, with sentinel lymph node biopsy, or by triage to lymphadenectomy through intraoperative pathologic evaluation of the uterus.

Although selection of the optimal approach for evaluating lymph nodes in AEH is beyond the scope of this article, each method carries additional risk compared with hysterectomy alone, related to time under anesthesia, intraoperative morbidity, and/or postoperative sequelae (eg, lymphedema). For the 62% of patients who do not have endometrial carcinoma, these additional risks are arguably unnecessary.

Under a selective referral strategy, approximately 38% of patients who do not opt for surgery with a gynecologic oncologist would be referred for consultation with a diagnosis of endometrial carcinoma after hysterectomy. At that time, the gynecologic oncologist should decide whether lymphadenectomy is required as a second surgery.

For tumors otherwise confined to the uterus, nodal metastases may necessitate chemotherapy rather than radiation therapy alone or observation.¹⁷ Again, while it is beyond the scope of this discussion to make definitive

recommendations regarding who should undergo a second procedure or what this procedure should entail, available data suggest that only a minority of patients will merit additional surgery.

Importantly, if lymph node evaluation is not done at the time of the hysterectomy, the relevant risk to patients is the potential morbidity associated with a possible second surgery, rather than the percentage of patients who, if they were to undergo such a surgery, would have positive lymph nodes.⁸

The magnitude of the risk of perioperative complication depends on the route of surgery (eg, minimally invasive versus open) as well as the patient's medical comorbidities, and this may vary dramatically from patient to patient.¹⁸ If lymphadenectomy is performed as a second procedure, the risk of lymphedema may be as high as 38% because the less morbid sentinel lymph node biopsy is no longer possible.^{19,20} Additionally, the time needed to schedule and recover from a second surgery could delay the initiation of adjuvant radiation or chemotherapy if needed.

Preoperative imaging, if any, along with tumor characteristics including size, grade, depth of myometrial invasion, and presence of lymphovascular space invasion (LVSI) will be available to the consulting gynecologic oncologist from the initial pathology report or on subsequent review of slides. Patients

TABLE**Requirements for surgical treatment of atypical endometrial hyperplasia by a nononcologic surgeon****Requirements**

- Patient is a surgical candidate based on review of medical and surgical history.
- Patient does not desire fertility preservation.
- Patient has been counseled regarding risk of occult malignancy (~38%) and possible need for second surgery (~2-6%).
- Surgeon has the ability to offer minimally invasive surgical techniques (eg, robot-assisted/traditional laparoscopy, vaginal hysterectomy).
- Surgeon has sufficient surgical volume to offer women undergoing hysterectomy optimal clinical outcomes.
- Surgical center has resources to manage potential perioperative complications.

Shalowitz. Surgical treatment and referral for atypical endometrial hyperplasia. Am J Obstet Gynecol 2019.

with grades 1–2 endometrioid tumors, less than 2 cm in size, and invading less than 50% of the myometrial depth have a negligible risk of nodal metastases and therefore do not need additional surgery.⁵

Two of the largest case series of hysterectomy for AEH reported that 84–95% of endometrial cancers detected are grade 1 or grade 2 with <50% myometrial invasion.^{21,22} Granting that some of these patients may merit consideration of lymphadenectomy based on tumor characteristics (eg, size or lymphovascular space invasion), only approximately 2–6% of patients with AEH on preoperative biopsy may be at risk for a second procedure. (Assuming that 38% of cases of AEH have carcinoma on final pathology, and 5–16% of carcinomas are grade 3 or invade >50% of the myometrium; $38\% \times 5\% - 38\% \times 16\% \approx 2\% - 6\%$).

There may additionally be unusual circumstances in which the ovaries are conserved at the time of initial surgery, but oophorectomy is considered as part of a second surgical procedure. Although in general ovarian conservation may offer improved survival outcomes for younger women with benign disease and low-grade endometrioid carcinoma,²³ some patients may opt for oophorectomy after discussion of the possibility of synchronous or metastatic ovarian malignancy.²⁴

Access to care

Decisions regarding the triage of AEH may substantially affect the burdens

patients experience in seeking surgical care. The residents of 36% of counties, accounting for 9% of the adult female population in the United States, live farther than 50 miles from the nearest gynecologic oncologist.²⁵

Patients seeking gynecologic oncology care from these low-access counties may find the cost, time, and logistics required for travel difficult. Indeed, approximately 25% of patients would prefer not to travel 50 miles for gynecologic cancer care, even if surgery at a more distant facility is accompanied by a substantial survival benefit.²⁶ Transfer of care also reliably incurs delays related to scheduling of initial consultation and surgery, which could be exacerbated by transportation logistics if significant travel is required.

Regardless of geographic factors, a significant minority of women may not be able to see a gynecologic oncologist expeditiously as a consequence of their insurance: 27% of plans available on insurance exchanges nationally do not include a gynecologic oncologist in their list of covered providers.²⁷ The outcomes of patients with endometrioid endometrial carcinomas that may exist concurrently with AEH are time sensitive; delays to surgical treatment of 8 weeks or more are associated with worsened survival,^{28,29} and delays between surgery and adjuvant radiation therapy may increase the risk for recurrent disease.³⁰

Conversely, patients who undergo surgery with their primary gynecologist or another, local gynecologic surgeon

may be treated closer to their homes and might avoid many of the challenges associated with seeking subspecialty care. Although strategies to expedite referral and evaluation are invaluable when needed, 62% of patients with a preoperative diagnosis of AEH do not have cancer and may not derive enough benefit from gynecologic oncologic evaluation to justify the burdens of pursuing subspecialty care.

Additionally, under a policy of selective referral, the burdens of travel may be further reduced postoperatively by utilizing telemedical consultation with gynecologic oncologists, when available and appropriate.³¹ For patients who opt for close clinical follow-up alone following consultation, a face-to-face encounter may not be necessary.

Selection of an approach

Physicians may decide to implement a strategy of universal referral to a gynecologic oncologist for surgical treatment of AEH based on personal practice pattern, relatively easy access to a gynecologic oncologist, or if high-quality nononcologic gynecologic surgical care is not available. If selective referral is used, surgical treatment for AEH should not be undertaken by a nononcologic gynecologist without a clear and open discussion of the risks and benefits of this approach.

This discussion must occur prior to surgery and ideally should occur prior to referral for surgery if the diagnosing provider is not the potential surgeon. Physicians should discuss the implications of the diagnosis of AEH (ie, that there is a moderate chance of a concurrent endometrial malignancy), and the advantages and disadvantages of immediate vs possible postoperative referral to a cancer specialist.

Attention should be paid to the possibility of needing a second surgery and its associated morbidity as well as any significant logistical differences in opting for immediate vs potential postoperative referral (eg, if there is a high-volume nononcologic gynecologic surgeon locally, but the closest gynecologic oncologist is 50 miles distant). Some patients may opt for surgery with their

trusted primary gynecologist or prefer surgery closer to home. Others may prefer a definitive single surgery with an oncologist, understanding that, *ex post*, treatment by a cancer specialist may not have been necessary.

Regardless of their final decisions, we anticipate that offering patients the option of postoperative triage for gynecologic oncology consultation will improve the perception of the decision-making process and potentially improve follow-up with oncologists when additional consultation is required. Additionally, appropriate utilization of a selective referral strategy for AEH may open additional avenues for care when access to a gynecologic oncologist is limited.

The decision to adopt universal or selective referral strategies may also be undertaken at the level of health systems rather than by individual clinicians, based on volume considerations and the availability of high-quality gynecologic surgeons. Routine referral of AEH to nononcologic surgeons, as is recommended in the United Kingdom, is inconsistent with contemporary referral practices in the United States where there has been a trend toward increasing referral of benign cases to oncologic surgeons.³² As such, the approach recommended by the Royal College of Obstetricians and Gynaecologists would be culturally difficult to adopt in the United States. Furthermore, consistent with the strong tradition of patient-centered medicine in the United States, we would argue that patients with AEH should always be at least offered the opportunity to avoid the possibility, even if small, of a second surgery for endometrial cancer through access to a gynecologic oncologist. As a rule, shared decision-making is appropriate when patients' priorities may vary when selecting a treatment plan.

In summary, universal referral of patients to gynecologic oncologists for surgical treatment of AEH is always acceptable as standard practice. However, selective referral of only those patients who have evidence of cancer after hysterectomy is also reasonable, provided that standards for high-quality care are

met for the initial surgery. Importantly, patients who are candidates for fertility preservation, desire medical management, or may not be surgical candidates should be referred for consultation with a gynecologic oncologist.

Additionally, expert surgical consultation is indicated for patients with AEH who may require complex medical or surgical care in the perioperative period. In appropriately selected cases, a selective referral strategy may offer patients increased options for surgical gynecologic care without compromising oncologic outcomes. In regions in which gynecologic oncology care is not easily accessible, selective referral may also reduce delays between diagnosis and surgical treatment and potentially improve outcomes for women with this disease. ■

ACKNOWLEDGMENT

We gratefully acknowledge Dr Michael Muto for helpful comments on an earlier draft of this manuscript.

REFERENCES

1. Reed SD, Newton KM, Clinton WL, et al. Incidence of endometrial hyperplasia. *Am J Obstet Gynecol* 2009;200:678.e1-6.
2. Emons G, Beckmann MW, Schmidt D, Mallmann P. Uterus Commission of the Gynecological Oncology Working Group (AGO). New WHO classification of endometrial hyperplasias. *Geburtshilfe Frauenheilkd* 2015;75:135-6.
3. Rakha E, Wong SC, Soomro I, et al. Clinical outcome of atypical endometrial hyperplasia diagnosed on an endometrial biopsy: institutional experience and review of literature. *Am J Surg Pathol* 2012;36:1683-90.
4. Committee on Gynecologic Practice, Society of Gynecologic Oncology. Committee opinion no. 631. *Obstet Gynecol* 2015;125:1272-8.
5. AlHilli MM, Podratz KC, Dowdy SC, et al. Preoperative biopsy and intraoperative tumor diameter predict lymph node dissemination in endometrial cancer. *Gynecol Oncol* 2013;128:294-9.
6. Touhami O, Grégoire J, Renaud M-C, Sebastianelli A, Grondin K, Plante M. The utility of sentinel lymph node mapping in the management of endometrial atypical hyperplasia. *Gynecol Oncol* 2018;148:485-90.
7. Wright JD, Chen L, Gabor L, et al. Patterns of specialty-based referral and perioperative outcomes for women with endometrial cancer undergoing hysterectomy. *Obstet Gynecol* 2017;130:81-90.
8. Costales AB, Schmeler KM, Broaddus R, et al. Clinically significant endometrial cancer risk following a diagnosis of complex atypical hyperplasia. *Gynecol Oncol* 2014;135:451-4.
9. Diaz-Montes TP, Zahurak ML, Giuntoli RL, Gardner GJ, Bristow RE. Uterine cancer in Maryland: impact of surgeon case volume and other prognostic factors on short-term mortality. *Gynecol Oncol* 2006;103:1043-7.
10. Trimble CL, Method M, Leitao M, et al. Management of endometrial precancers. *Obstet Gynecol* 2012;120:1160-75.
11. Royal College of Obstetricians and Gynaecologists/British Society for Gynaecological Endoscopy. 2016. Green-top guideline no. 67: management of endometrial hyperplasia. Available at: https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_67_endometrial_hyperplasia.pdf. Accessed December 26, 2018.
12. Cancer Care Ontario. Endometrial cancer treatment and follow-up pathway map. Disease pathway management 2017. Available at: <https://www.cancercareontario.ca/sites/ccocancercare/files/assets/CCOEndometrialTreatmentFollowUpPathway1.pdf>. Accessed December 26, 2018.
13. Mowat A, Maher C, Ballard E. Surgical outcomes for low-volume vs high-volume surgeons in gynecology surgery: a systematic review and meta-analysis. *Am J Obstet Gynecol* 2016;215:21-33.
14. Wallenstein MR, Ananth CV, Kim JH, et al. Effect of surgical volume on outcomes for laparoscopic hysterectomy for benign indications. *Obstet Gynecol* 2012;119:709-16.
15. Rogo-Gupta LJ, Lewin SN, Kim JH, et al. The effect of surgeon volume on outcomes and resource use for vaginal hysterectomy. *Obstet Gynecol* 2010;116:1341-7.
16. Wright JD, Herzog TJ, Siddiq Z, et al. Failure to rescue as a source of variation in hospital mortality for ovarian cancer. *J Clin Oncol* 2012;30:3976-82.
17. Koh W-J, Abu-Rustum NR, Bean S, et al. Uterine neoplasms, version 1.2018. National Comprehensive Cancer Network clinical practice guidelines in oncology. *J Natl Compr Cancer Netw* 2018;16:170-99.
18. American College of Surgeons/National Surgical Quality Improvement Program. Surgical risk calculator. Available at: <https://riskcalculator.facs.org/RiskCalculator/index.jsp>. Accessed December 26, 2018.
19. Lindqvist E, Wedin M, Fredrikson M, Kjølhede P. Lymphedema after treatment for endometrial cancer—a review of prevalence and risk factors. *Eur J Obstet Gynecol Reprod Biol* 2017;211:112-21. d.
20. Todo Y, Yamamoto R, Minobe S, et al. Risk factors for postoperative lower-extremity lymphedema in endometrial cancer survivors who had treatment including lymphadenectomy. *Gynecol Oncol* 2010;119:60-4.
21. Trimble CL, Kauderer J, Zaino R, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia. *Cancer* 2006;106:812-9.

- 22.** Suh-Burgmann E, Hung Y-Y, Armstrong MA. Complex atypical endometrial hyperplasia. *Obstet Gynecol* 2009;114:523–9.
- 23.** Matsuo K, Machida H, Shoupe D, et al. Ovarian conservation and overall survival in young women with early-stage low-grade endometrial cancer. *Obstet Gynecol* 2016;128:761–70.
- 24.** Walsh C, Holschneider C, Hoang Y, Tieu K, Karlan B, Cass I. Coexisting ovarian malignancy in young women with endometrial cancer. *Obstet Gynecol* 2005;106:693–9.
- 25.** Shalowitz DI, Vinograd AM, Giuntoli RL. Geographic access to gynecologic cancer care in the United States. *Gynecol Oncol* 2015;138:115–20.
- 26.** Shalowitz DI, Nivasch E, Burger RA, Schapira MM. Are patients willing to travel for better ovarian cancer care? *Gynecol Oncol* 2018;148:42–8.
- 27.** Shalowitz DI, Huh WK. Access to gynecologic oncology care and the network adequacy standard. *Cancer* 2018;124:2677–9.
- 28.** Shalowitz DI, Epstein AJ, Buckingham L, Ko EM, Giuntoli RL. Survival implications of time to surgical treatment of endometrial cancers. *Am J Obstet Gynecol* 2017;216:268.e1–18.
- 29.** Elit LM, O’Leary EM, Pond GR, Seow H-Y. Impact of wait times on survival for women with uterine cancer. *J Clin Oncol* 2014;32:27–33.
- 30.** Cattaneo R, Hanna RK, Jacobsen G, Elshaikh MA. Interval between hysterectomy and start of radiation treatment is predictive of recurrence in patients with endometrial carcinoma. *Int J Radiat Oncol* 2014;88:866–71.
- 31.** Shalowitz DI, Smith AG, Bell MC, Gibb RK. Teleoncology for gynecologic cancers. *Gynecol Oncol* 2015;139:172–7.
- 32.** Barber EL, Rossi EC, Alexander A, Bilimoria K, Simon MA. Benign hysterectomy performed by gynecologic oncologists: is selection bias altering our ability to measure surgical quality? *Gynecol Oncol* 2018;151:141–4.