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Clinically Significant Endometrial Cancer Risk Following a Diagnosis of Complex Atypical Hyperplasia

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Abstract

Objectives—Because of the frequent detection of carcinoma in surgical specimens after hysterectomy for endometrial complex atypical hyperplasia (CAH), it has been suggested that patients with a preoperative diagnosis of CAH be referred to gynecologic oncology for potential lymphadenectomy. However, the risk of lymph node metastasis in such patients is unknown. We sought to determine the risk of endometrial cancer and to estimate the risk of lymphatic spread in women with a preoperative diagnosis of CAH.

Study Design—We retrospectively reviewed the medical records of 150 consecutive patients with a preoperative diagnosis of CAH who subsequently underwent hysterectomy. Clinical characteristics and pathologic information were abstracted. Risk of lymphatic spread was modeled using previously published criteria and nomograms.

Results—Fifty-five of the 150 patients (36.7%) had an incidental endometrial carcinoma at the time of hysterectomy. Among patients with a preoperative office biopsy compared to dilation and curettage, the rate of an incidental finding of cancer was 43.5% and 28.1%, respectively (p=0.054). Of patients with cancer, 1 (1.8%) had a grade 3 endometrial carcinoma, 4 (7.3%) had lymphovascular space involvement, and 6 (10.9%) had deep (>50%) myometrial invasion. For the 10 patients who underwent lymphadenectomy, one (10%) had lymph node metastases. Based on

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multiple models, the estimated risk of lymph node spread was 1.6-2.1% for all women with a preoperative diagnosis of CAH and 4.4-6.8% for the 55 women with endometrial cancer.

Conclusions—Given the high rates of underlying endometrial cancer and the potential need for lymphadenectomy, care for patients with a preoperative diagnosis of CAH desiring definitive management with hysterectomy should be referred to a gynecologic oncologist.

INTRODUCTION

Complex atypical hyperplasia is a benign condition of the endometrium characterized by an increased gland/stroma ratio, abnormal glandular architecture, and nuclear atypia. This abnormality may progress to or co-exist with endometrial cancer. In the United States, the incidence of endometrial cancer is 23 cases per 100,000 women per year, whereas the incidence of complex atypical hyperplasia is 17 cases per 100,000 women per year. (1) Among women with complex atypical hyperplasia diagnosed on preoperative endometrial biopsy, 17-50% are ultimately found to have concomitant carcinoma; thus, for women who are appropriate surgical candidates and who are finished with childbearing, total hysterectomy is recommended. (2-4)

Due to the risk of detection of carcinoma in surgical specimens following hysterectomy, the American Congress of Obstetricians and Gynecologists (ACOG) recommends that patients with a preoperative diagnosis of complex atypical hyperplasia be referred to a gynecologic oncologist. (5) Presumably, a gynecologic oncologist would be prepared to perform surgical staging in patients found intraoperatively to have endometrial cancer. Many gynecologic oncologists rely on intraoperative algorithms as decision tools for determining which patients with endometrial cancer actually require lymphadenectomy. Typically, patients thought to be at low risk for lymphatic spread, and therefore not requiring removal of lymph nodes, are those with grade 1 or 2 endometrioid adenocarcinomas invading less than 50% of the myometrium and with tumors ≤2 cm in diameter. (6)

Anecdotal evidence suggests that most women with an incidental finding of endometrial cancer intra- or postoperatively after a preoperative diagnosis of complex atypical hyperplasia would meet those low-risk criteria and therefore not require involvement of a gynecologic oncologist in their care. However, the risk of lymph node spread in all women with a preoperative diagnosis of complex atypical hyperplasia has never been assessed. The objectives of this study were to determine the risk of endometrial cancer and to estimate the risk of lymphatic spread in women with a preoperative diagnosis of complex atypical hyperplasia.

MATERIALS AND METHODS

After obtaining approval from the Institutional Review Board of The University of Texas MD Anderson Cancer Center, we performed a retrospective review of all patients with a preoperative diagnosis of complex atypical hyperplasia who subsequently underwent hysterectomy during the period from January 1, 1995, through April 1, 2013. Eligible patients were identified by a search of the pathology database at our institution. All patients had the initial diagnosis made by office endometrial biopsy or operative curettage. All

pathology slides were reviewed by one of seven gynecologic pathologists at our institution. Patients with a preoperative tissue diagnosis of endometrial cancer, simple hyperplasia, complex hyperplasia without atypia, and complex atypical hyperplasia- cannot rule out malignancy were excluded. Surgical management was at the discretion of the primary surgeon, and surgical approaches included vaginal, open, laparoscopic, and robotic. The addition of lymphadenectomy was also at the surgeon's discretion.

One hundred fifty patients were identified who met the inclusion criteria. Medical records were reviewed for patient demographics, including age at diagnosis, body mass index, comorbidities, time to definitive surgical intervention, surgical management, and pathologic findings. If intraoperative frozen section information was available, this was also abstracted. Patients were then classified as underweight (BMI < 18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25.0-29.9 kg/m^2), obese (BMI 30.0-34.9 kg/m^2), or morbidly obese (BMI ≥ 35.0 kg/m^2) according to definitions from the National Institutes of Health. To estimate the risk of lymph node metastases we utilized data from 3 previously published studies. (7-9) First, patients were classified on the basis of criteria established by the Gynecologic Oncology Group in a prospective study evaluating the risk of lymph node spread in women with endometrial cancer (GOG-33). (7) Patients were classified as low risk if they had histologic grade 1 disease limited to the endometrium and no intraperitoneal disease. Patients were classified as moderate risk if they had less than or equal to two-thirds myometrial invasion and/or histologic grade 2 or 3 disease without intraperitoneal disease. These patients were subclassified as moderate risk with 1 factor or moderate risk with both factors. Finally, patients were classified as high risk if they had intraperitoneal disease or greater than two-thirds myometrial invasion. These patients were subclassified as high risk with deep invasion only, intraperitoneal disease only, or both factors. A previously published decision tree was then utilized to determine overall risk of pelvic and paraaortic lymph node spread. (10) Second, risk of lymph node spread was estimated utilizing a nomogram published by Bendifallah et al. (8) This nomogram predicts the risk of lymph node spread on the basis of patient age and race, tumor histology and grade, and depth of invasion/cervical involvement. Third, a second nomogram, published by AlHilli et al., (9) was utilized to predict the risk of lymph node metastases. This nomogram incorporates tumor grade, depth of invasion/cervical involvement, and lymphovascular space invasion into a risk-scoring system and is based on prospective data collected at The Mayo Clinic. The "Mayo Criteria" utilized prospective data to guide intraoperative decision making on lymphadenectomy, which included International Federation of Gynecology and Obstetrics grade 1 or 2 endometrioid corpus cancer with greatest surface dimension ≤2 cm, myometrial invasion ≤50%, and no intraoperative evidence of macroscopic disease as markers for only performing simple hysterectomy. (6) Authors of both nomograms kindly provided statistical models to assist with our calculations.

To estimate the portion of patients that would potentially require postoperative radiation therapy, we utilized data from a Gynecologic Oncology Group phase III study evaluating adjuvant radiation therapy in women with endometrial adenocarcinoma (GOG-99). (11) Patients were classified as being at high intermediate risk (and therefore potentially requiring adjuvant radiation therapy) on the basis of 3 risk factors: 1) histologic grade 2 or 3 tumor, 2) presence of lymphvascular space invasion, and 3) greater than 50% myometrial

invasion. To be considered at high intermediate risk, patients greater than 70 years old required at least 1 risk factor, patients 50-70 years old required at least 2 risk factors, and patients less than 50 years old required all 3 risk factors. (11)

Fisher's exact test, the Mann-Whitney test, and the chi-squared test were used to evaluate differences between groups where appropriate. Missing data were coded as "unknown," and those data points were excluded from the analysis. Unless otherwise noted, *P* values were not adjusted for multiple comparisons. *P* values of less than 0.05 were considered statistically significant. All data were analyzed using SPSS 15.0 for Windows (SPSS, Inc., Chicago, IL).

RESULTS

Demographic information for the 150 patients in the study is shown in Table 1. The median age at diagnosis was 55 years (range 27-89 years). The median body mass index was 33.2 kg/m^2 (19.4-79.5 kg/m^2). The preoperative diagnosis of complex atypical hyperplasia was made by office endometrial pipelle biopsy in 85 patients (56.7%), dilation and curettage in 64 patients (42.7%), and unknown method in 1 patient (0.6%). Surgical management included total abdominal hysterectomy via a laparotomy in 63 patients (42.0%); a minimally invasive procedure in the form of laparoscopic-assisted vaginal hysterectomy, total laparoscopic hysterectomy, or robotic-assisted total laparoscopic hysterectomy in 72 patients (48.0%); and total vaginal hysterectomy in 6 patients (4.0%). The surgical approach was unknown in 9 patients (6.0%). Lymphadenectomy was performed in 10 patients (6.7%).

Fifty-five patients (36.7%) were found to have endometrioid adenocarcinoma at hysterectomy. The rate of an incidental finding of cancer on final pathology review of the hysterectomy specimen was 43.5% (37 of 85 patients) among patients who had an office endometrial biopsy, compared to 28.1% (18 of 64 patients) among patients who underwent dilation and curettage (p=0.054). Among the patients for whom BMI was known, cancer was diagnosed in 10 of 23 normal-weight patients (43.5%), 10 of 25 overweight patients (40.0%), 6 of 17 obese patients (35.3%), and 15 of 57 morbidly obese patients (26.3%). A total of 99 patients (66.0%) had intraoperative frozen section examination performed. Among the 55 patients with a final diagnosis of cancer, 37 (67%) had intraoperative frozen section analysis. Intraoperative frozen section examination revealed no disease in 1 patient (1.8%), complex atypical hyperplasia in 11 patients (20.0%), and cancer in 25 patients (45.5%). In our study, 14 patients (25.5%) found to have cancer on final pathology had disease that would have warranted complete surgical staging with lymphadenectomy according to the Mayo criteria. (6,12) However, only 5 (35.7%) of these patients underwent complete surgical staging.

Of the 55 patients found to have cancer, 1 patient (1.8%) had a mixed serous and FIGO grade 3 endmetrioid adenocarcinoma, 4 (7.3%) had lymphovascular space invasion, and 7 (10.9%) had greater than 50% or deep myometrial invasion. (Table 2) Of the 30 patients with cancer (54.5%) in whom peritoneal washings were obtained, 1 patient (3.3%) had positive peritoneal cytology. Ten patients underwent lymph node dissection and 1 (10%) was found to have metastatic disease in the obturator nodes. According to the GOG-33

criteria for risk of lymph node metastases, 16 patients (29.1%) were classified as low risk, 23 patients (41.8%) as moderate risk with 1 risk factor, 12 patients (21.8%) as moderate risk with 2 risk factors, 2 patients (3.6%) as high risk with deep invasion only, and 1 patient (1.8%) as high risk with intraperitoneal disease only (ovarian involvement).

For the entire cohort of 150 patients, the estimated risk of lymph node spread according to the GOG-33 criteria was 1.6% for pelvic nodes and 0.7% for paraaortic nodes. (Table 3) According to the Bendifallah nomogram (8), the risk of any lymph node spread was 1.9%. According to the AlHilli nomogram (9), the risk of any lymph node spread was 2.1%. According to the GOG-99 data, 9 patients (6%) met the criteria for high-intermediate-risk disease.

For the 55 patients with a final diagnosis of endometrial cancer, the estimated risk of lymph node spread according to the GOG-33 criteria was 4.4% for pelvic nodes and 2.1% for paraaortic nodes. According to the Bendifallah nomogram (8), the risk of any lymph node spread was 6.8%. According to the AlHilli nomogram (9), the risk of any lymph node spread was 5.0%. According to the GOG-99 data, 9 patients (16%) met the criteria for high-intermediate-risk disease.

According to GOG-33 criteria, 15 patients have a risk of lymph node spread ≥5%, and 3 have a risk of lymph node spread ≥10% with risk for lymph node spread as high as 33%. According to the Bendifallah nomogram (8), 13 patients have a risk of lymph node spread ≥5%, and 8 have a risk of lymph node spread ≥10% with one patient having a risk for lymph node spread of 35%. According to the AlHilli nomogram (9), 11 patients have a risk of lymph node spread ≥5%, and 9 have a risk of lymph node spread ≥10% with risk for lymph node spread as high as 49.4%. (Table 4)

DISCUSSION

In our cohort, 37% of patients with complex atypical hyperplasia diagnosed on a preoperative office endometrial biopsy or dilation and curettage had invasive carcinoma detected in the final hysterectomy specimen. Furthermore, estimates based on previously published criteria and nomograms indicated that up to 2.1% of all patients with a preoperative diagnosis of complex atypical hyperplasia and up to 6.8% of those subsequently diagnosed with cancer would be likely to have lymph node involvement. These findings suggest that prior to hysterectomy, these patients may benefit from seeing a gynecologic oncologist for both risk counselling and a lymphadenectomy if needed at the time of hysterectomy. The high rate of unrecognized cancer in patients with a preoperative diagnosis of complex atypical hyperplasia stems partly from both the scant amount of tissue often obtained at biopsy and the difficulty in differentiating this diagnosis from grade 1 adenocarcinoma on the basis of histology. (13-15) In a Gynecologic Oncology Group study, 3 gynecologic pathologists reviewed 306 biopsy or curettage specimens identified as complex atypical hyperplasia on final pathology, and 29% were upstaged to adenocarcinoma. (3) Overall, that study found that 43% of patients with a preoperative diagnosis of complex atypical hyperplasia had an invasive carcinoma found on final

pathology. This rate correlates closely with our finding that 37% of such patients had carcinoma as an incidental finding in hysterectomy specimens.

Previously published data concerning whether dilation and curettage is more accurate than office endometrial biopsy in detecting cancer among women with complex atypical hyperplasia are limited. Suh-Burgmann et al. (16) reviewed their experience of 724 patients with a preoperative diagnosis of complex atypical hyperplasia. The risk of cancer was significantly lower for women who had a dilation and curettage than for women who had an office endometrial biopsy: 30% vs. 45% ($p<0.001$) This observation correlates closely with our observation that the rate of cancer in the hysterectomy specimen was 29% among patients who were initially evaluated by dilation and curettage, compared to 44% in women who had an office endometrial biopsy. Although our study was not powered for this outcome and did not reach statistical significance, the difference would likely have been significant with a larger sample size. The decision to perform curettage often hinges on patient factors such as body habitus, cervical stenosis, or intolerance to office biopsy. Although the rate of incidental cancer at the time of hysterectomy is high with either preoperative sampling approach, given the higher rate with office biopsy, one should perform an operative curettage prior to conservative management and should consider this prior to definitive hysterectomy.

In our study, 14 patients (25.5%) found to have cancer on final pathology had disease that would have warranted complete surgical staging with lymphadenectomy according to the Mayo criteria. (6, 12) However, only 5 (35.7%) of these patients underwent complete surgical staging. Although only 1 patient in our study was found to have positive lymph node involvement, we believe this number would have increased if more patients had undergone lymphadenectomy. An important consideration concerning lymphadenectomy is that if lymphadenectomy is undertaken, adequate sampling must be done to make the procedure worthwhile. For this reason, involvement of a gynecologic oncologist in the intraoperative care of patients with a preoperative diagnosis of endometrial complex atypical hyperplasia iswarranted. If these patients are referred postoperatively after a diagnosis of cancer, the dilemma arises of whether or not to return to the operating room for surgical staging. Our findings from the current study indicate that without surgical staging, 16% of these patients may simply receive adjuvant therapy based on GOG-99 criteria, which would represent overtreatment in women with node-negative disease.

Although the International Federation of Obstetrics and Gynecology recommended surgical staging for endometrial cancer patients in 1988, controversy still remains concerning the role of lymphadenectomy. Specifically, two large randomized trials suggested that pelvic lymphadenectomy had no clear impact on survival outcomes, but increased morbidity. (17, 18) In summary, a total of 1922 patients were randomly assigned to evaluate whether the addition of pelvic, and para-aortic only in selected cases, lymphadenectomy improved survival outcomes. The results showed that lymphadenectomy did not improve disease-free survival (CI, 0.96-1.58) and overall survival (CI, 0.81-1.43). However, the majority of gynecologic oncologists in the United States use lymphadenectomy in patients with endometrial cancer to guide their decision on postoperative adjuvant therapy.

The limitations of this study are similar to those associated with all retrospective studies and include potential biases, especially in regard to the surgeon's decision to order intraoperative frozen section. Of the patients with a final diagnosis of cancer, only two-thirds had an intraoperative pathology consultation. Multiple studies have evaluated the concordance between intraoperative and postoperative pathologic evaluation including histologic subtype, depth of myometrial invasion, and grade and have showing concordances ranging from 78-98%. (10, 19-20) We believe our findings support routine intraoperative frozen section evaluation for women with a preoperative diagnosis of complex atypical hyperplasia. Also, these data are from a single large referral center, which could introduce selection bias as patients who are referred could be the patients for whom final pathology results are more severe than expected. Finally, the 3 studies utilized to model the risk of lymph node metastases have not been externally validated. However, the 3 models yielded similar estimates of risk of lymph node spread, which was reassuring.

Our hypothesis that women with an incidental finding of endometrial cancer after a preoperative diagnosis of complex atypical hyperplasia would have low-risk disease was not universally true. As many as 37% of women with a preoperative diagnosis of uterine complex atypical hyperplasia ultimately are found to have an invasive adenocarcinoma; and in these patients, the modeled risk of lymph node disease was as high as 6.8%. Given both the high risk of an incidental carcinoma and the significant risk of lymph node disease in patients with carcinoma, we believe these patients should be referred to a gynecologic oncologist and be involved in the surgical care of women with a preoperative diagnosis of endometrial complex atypical hyperplasia.

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Research Highlights

- A pre-hysterectomy diagnosis of endometrial complex atypical hyperplasia carries a substantial risk for invasive cancer and lymph node spread.
- The risk of lymph node spread may be as high as 6.8% in some patients with complex atypical hyperplasia.
- A gynecologic oncologist should be involved in the preoperative counseling of women with a diagnosis of endometrial complex atypical hyperplasia.

Table 1

Patient Characteristics

Median age at diagnosis, years (range)	55 (27-89)
Median body mass index, kg/m^2 (range)	33.2 (19.4-79.5)
Weight class, n (%)	
Underweight (<18.5 kg/m^2)	3 (2.0)
Normal weight (18.5-24.9 kg/m^2)	23 (15.3)
Overweight (25.0-29.9 kg/m^2)	25 (16.7)
Obese(30.0-34.9 kg/m^2)	17 (11.3)
Morbidly obese (≥35.0 kg/m^2)	57 (38.0)
Unknown	25 (16.7)
Race/ethnicity, n (%)	
White	110 (73.3)
African American	13 (8.7)
Hispanic	16 (10.7)
Asian	8 (5.3)
Unknown	3 (2.0)

Table 2

Relationship of tumor grade and depth of invasion for 55 patients with final diagnosis of invasive cancer

	No Invasion	<50% invasion	≥50% invasion
Grade 1	16	18	1
Grade 2	4	10	5
Grade 3	0	0	1

Table 3

Modeled risk of lymph node spread in women with preoperative diagnosis of complex atypical hyperplasia and final diagnosis of invasive cancer

Algorithm	All patients (n=150)	Endometrial cancer patients (n=55)
GOG-33 Criteria [1]	1.6% pelvic nodes 0.7% aortic nodes	4.4% pelvic nodes 2.1% aortic nodes
Bendifallah nomogram [2]	1.9% any node	6.8% any node
AlHilli nomogram [3]	2.1% any node	5.0% any node

Table 4

Number and percentage of patients with ≥5% and ≥10% modeled risk of nodal spread

Algorithm	≥5% Risk of Nodal Spread			≥10% Risk of Nodal Spread		
	n	% all patients (n=150)	% endometrial cancer patients (n=55)	n	% all patients (n=150)	% endometrial cancer patients (n=55)
GOG-33 Criteria [1]	15	10.0	27.3	3	2.0	5.5
Bendifallah nomogram [2]	13	8.7	23.6	8	5.3	14.5
AlHilli nomogram [3]	11	7.3	20.0	9	6.0	10.9

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