

Significance of Concurrent Endometrial Cancer in Women With a Preoperative Diagnosis of Atypical Endometrial Hyperplasia

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Abstract

Objectives: Our objectives were (1) to review the rate of concurrent endometrial cancer in patients with a preoperative diagnosis of atypical endometrial hyperplasia (AEH); (2) to determine the proportion of patients with concurrent endometrial cancer who have high-risk disease; and (3) to re-evaluate our surgical management of AEH.

Methods: We performed a retrospective chart review of all patients who had surgery on the basis of a preoperative diagnosis of atypical endometrial hyperplasia between January 2001 and December 2006. Demographic data, the method of preoperative diagnosis, postoperative grade of tumour, and other postoperative findings were recorded. When applicable, this included cancer stage, lymph node status, and presence of lymphovascular space invasion. In postoperative review, patients were considered to be high risk if they had disease beyond the uterus or a combination of other risk factors.

Results: Of 70 patients, 25 (35.7%) were found to have concurrent endometrial cancer. This was higher than the commonly accepted rate of 25% ($P = 0.03$). Of the 25 patients upgraded, 4 (16%) had high-risk cancer on final pathologic evaluation.

Conclusion: Simple hysterectomy in women with AEH may result in inadequate surgical management. Simple methods are required to identify patients with a preoperative diagnosis of AEH who may harbour significant cancers.

Méthodes : Nous avons procédé à une analyse rétrospective des dossiers de toutes les patientes ayant subi une chirurgie en fonction d'un diagnostic préopératoire d'hyperplasie endométriale atypique entre janvier 2001 et décembre 2006. Les données démographiques, le mode de diagnostic préopératoire, le grade postopératoire de la tumeur, ainsi que d'autres résultats postopératoires ont été consignés. Le cas échéant, cela comprenait le stade du cancer, l'état des ganglions lymphatiques et la présence d'une invasion de l'espace lymphovasculaire. Dans le cadre de l'analyse postopératoire, les patientes étaient considérées comme étant exposées à un risque élevé lorsque la maladie s'étendait au-delà de l'utérus ou en présence d'une combinaison d'autres facteurs de risque.

Résultats : Chez 25 (35,7 %) des 70 patientes, nous avons constaté la présence d'un cancer concomitant de l'endomètre; cela représente un taux plus élevé que ce qui est habituellement accepté, soit de 25 % ($P = 0,03$). L'évaluation pathologique finale a révélé que quatre (16 %) de ces 25 patientes présentaient un cancer entraînant des risques élevés.

Conclusion : L'exécution d'une simple hystérectomie chez les femmes présentant une HEA peut se traduire en une prise en charge chirurgicale inadéquate. Des méthodes simples sont requises pour identifier les patientes présentant un diagnostic préopératoire d'HEA qui pourraient également présenter des cancers significatifs.

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Résumé

Objectifs : Nos objectifs étaient (1) d'analyser le taux de cancer concomitant de l'endomètre chez les patientes présentant un diagnostic préopératoire d'hyperplasie endométriale atypique (HEA); (2) de déterminer la proportion de patientes atteintes d'un cancer concomitant de l'endomètre qui présentent une maladie entraînant des risques élevés; et (3) de réévaluer notre prise en charge chirurgicale de l'HEA.

Key Words: Atypical endometrial hyperplasia, concurrent endometrial cancer, significant-risk cancer

Competing Interests: None declared.

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INTRODUCTION

Two issues must be considered in determining the optimal management of patients with a preoperative diagnosis of atypical endometrial hyperplasia. The first issue is the risk of AEH progressing to cancer; the second is the possibility that endometrial cancer is already present (concurrent EC). Although it seems widely accepted that 23% to 25% of patients with AEH will progress to cancer,^{1,2} the frequency and significance of concurrent EC remains controversial.³⁻¹⁰

The traditional view has been that concurrent EC is acceptably infrequent and of low importance in patients with

preoperative AEH.³⁻⁵ In 1993, Janicek et al. summarized the results of six studies in which 122 of 463 patients with AEH (26%) were found to have concurrent EC.⁶ All but one of 122 patients with concurrent EC had well-differentiated carcinomas confined to the uterus. Therefore, a simple hysterectomy and bilateral salpingo-oophorectomy became the standard surgical approach for management of patients with AEH.³⁻⁵

More recent reviews of patients with a preoperative diagnosis of AEH report both higher rates of concurrent EC and more significant disease postoperatively.⁶⁻¹⁰ In the Gynecologic Oncology Group study reported by Trimble et al., 123 of 289 patients (42.6%) with AEH had a postoperative diagnosis of EC.¹⁰ Of those patients with concurrent EC, 10.6% were found to have deep myometrial invasion. These findings suggest that a policy of conservative surgery for patients with preoperative AEH could result in a substantial proportion of patients receiving suboptimal surgery.

Patients found to have low risk endometrial cancers have a good prognosis irrespective of staging surgery or adjuvant treatment.¹¹⁻¹³ In contrast, patients with intermediate and high risk cancers have a worse prognosis, but this can be improved by adjuvant therapies.¹³⁻¹⁵ Therefore, in patients with AEH, it is important to identify the rate of concurrent EC and to assess the risk status of those patients found to have cancer. Given the wide discrepancy of results in the literature, we felt it was important to review the rate and significance of concurrent EC in our patients presenting with a preoperative diagnosis of AEH.

The objectives of the present review were (1) to determine the proportion of patients at our centre with a preoperative diagnosis of AEH who were found postoperatively to have concurrent EC; (2) to determine the proportion of those patients with concurrent EC found postoperatively who also had significant-risk tumours; and (3) to use this information to make recommendations regarding the surgical management of patients with AEH. We hypothesized that 35% of patients with preoperative AEH would be found postoperatively to have concurrent EC. Our null hypothesis was that the proportion of patients with concurrent EC

would be no higher than the most commonly reported rate of 25%.

METHODS

We carried out a retrospective review within the Saskatoon Health Region. We first identified the charts of patients who had undergone hysterectomy for atypical endometrial hyperplasia between January 2001 and December 2006. Data collected included age, BMI, presenting symptoms, the method used for preoperative diagnosis, and the time between preoperative diagnosis and surgery. We did not collect data on non-surgical management of AEH. Postoperative endpoints included the final diagnosis and the grade and stage of the tumour if cancer was found. In patients with concurrent EC, the presence or absence of lymph vascular space invasion and lymph node status was recorded.

Patients were categorized as low risk, intermediate risk, or high risk. We combined the intermediate and high risk groups to form a significant risk category, in order to quantify the clinical importance of current EC found in patients with a preoperative diagnosis of AEH. We anticipated that patients in our cohort would have surgery limited to HBSO because the presence of concurrent EC would only be found on final pathologic analysis of hysterectomy specimens. Therefore, for patients with presumed stage I disease we had to use a method of risk determination independent of lymph node status. The European Post Operative Radiation Therapy in Endometrial Cancer 2 (PORTEC 2) trial provided such a risk categorization scheme.¹⁶ The risk categories used in this review are summarized in Table 1.

Finally, we compared our results with those found in the literature, applying our category of "significant risk" to the results of other reviews to facilitate comparison.

A pathology review was intentionally omitted to ensure that results would reflect our community-based practice; therefore, the pathology recorded was that found on patient charts. We did not have a pathologist specifically assigned to gynaecologic pathology, nor was there a system in place for either preoperative or postoperative pathology review of gynaecologic oncology cases during the study period. Our pathologists used the criteria established by Kurman and Norris to diagnose AEH.⁵

There was no standard surgical approach to patients with atypical endometrial hyperplasia at our centre during the time under review, nor was intraoperative inspection of the uterus, with or without frozen section, routinely carried out.

Statistical analyses were carried out using SPSS for Windows (Version 15, Chicago IL). Student *t* tests were used to compare the age and BMI between patient groups. A chi-squared analysis was conducted to compare mode of

ABBREVIATIONS

AEH	atypical endometrial hyperplasia
BMI	body mass index
EC	endometrial cancer
HBSO	hysterectomy and bilateral salpingo-oophorectomy

Table 1. Risk categories for patients with endometrial cancer and unknown lymph node status

Risk category	Tumour grade and depth of invasion
Low risk	Grade 1 or 2 with no or less than 50% myometrial invasion (stage IA and IB)
Intermediate risk	Grade 1 or 2 with more than 50% myometrial invasion (stage IC) Grade 1 or 2 with cervical mucosal involvement (stage IIA) Grade 3 with less than 50% myometrial invasion (stage IA and IB)
High risk	Grade 1 or 2 with cervical stromal involvement (stage IIB) Grade 3 with more than 50% myometrial invasion (stage IC) All patients with disease beyond the uterus and cervix

Table 2. Comparison of mean age, BMI, and time to surgery between patients with postoperative AEH and those with concurrent EC

	Overall (SD)	AEH only (SD)	Concurrent EC (SD)	<i>P</i>
Age (years)	57.4 (10.8)	56.5 (10.3)	59.0 (11.7)	0.36
BMI	34.0 (8.6)	33.9 (8.8)	34.1 (8.4)	0.91
Mean time to surgery (days)	78	76	81	0.79

preoperative diagnosis, and binomial analysis of proportions was used to compare our rate of concurrent EC with the P^0 of 0.25.

RESULTS

In the Saskatoon Health Region between January 2001 and December 2006, a total of 102 patients underwent hysterectomy for endometrial hyperplasia. Of those, 32 (31.4%) had a preoperative diagnosis of simple hyperplasia and were excluded from the analysis. Patients with a preoperative diagnosis of AEH ($n = 70$) remained in the study group.

The average age and BMI for the group is shown in Table 2. There was no difference in mean age or BMI among patients found to have concurrent EC and those whose diagnosis remained AEH. The presenting symptom for 50 of the patients (71%) was postmenopausal bleeding. The mean time to surgery for the cohort as a whole was 78 days. There was no difference in time to surgery between patients with the final diagnosis of AEH (76 days) and those found to have concurrent EC (81 days; $P = 0.79$). The proportion of patients with concurrent EC was not different between patients diagnosed preoperatively by office endometrial biopsy and those who had dilatation and curettage (Table 3).

Overall, 25 of the 70 patients with a preoperative diagnosis of AEH (35.7%) had concurrent EC identified postoperatively. When categorized by postoperative tumour grade, 17 of the 25 (68%) had grade 1 disease and 8 of 25 (32%) had grade 2 disease. There were no cases of grade 3 disease. Nineteen of the 25 patients with concurrent EC (76%) had

myometrial invasion on final pathology. In most cases (79%; 15/19) the myometrial invasion was less than 50% (stage IB). Four of the 25 (16%) were categorized as having significant-risk cancers. Three of the patients had grade 2, stage IC disease and one had grade 2, stage IIA disease. No patients were identified with disease beyond the uterus. The grade and stage of patients with postoperative EC are summarized in Table 4.

DISCUSSION

In our referral centre, we found that nearly 36% of patients with a preoperative diagnosis of atypical endometrial hyperplasia had concurrent endometrial cancer. This statistic was significantly higher than the traditionally accepted rate of 25%⁶ and consistent with other more recent reviews.⁷⁻¹⁰ Sixteen percent of our patients with concurrent EC were also found to have significant-risk cancers. We interpreted these results to mean that managing all patients who have a preoperative diagnosis of AEH with routine HBSO may be suboptimal.

A summary of nine studies (including the present study) of AEH and concurrent EC is given in Table 5. The rate of concurrent EC ranged from 17% to 50%. Of the nine studies, eight described the proportion of patients with myometrial invasion, which ranged from 33% to 89%. Four of the studies provided information on the severity of concurrent EC, and two (the current study and that of Trimble et al.¹⁰) categorized patients according to risk. In the study of Trimble et al.,¹⁰ "high risk" lesions were defined as myoinvasive or grade 2 or 3 lesions, and 43 of 123 tumours

(35%) fell into this category. We applied our definition of significant-risk cancer to the three other studies reporting on severity of cancer,^{7,10,11} and found that the proportion of patients with significant-risk cancers ranged from 12.2%¹⁰ to 38.6%.⁷

Staging surgery for patients with concurrent EC in patients with preoperative AEH is important only if a substantial proportion of such patients harbour intermediate-risk or high-risk cancers. Surgical staging of patients with low-risk cancers has no significant impact on survival, and failing to identify these patients either preoperatively or intraoperatively will not adversely affect an already good prognosis.^{11–13} However, in patients with intermediate- and high-risk cancers, survival rates can be improved by adjuvant treatment tailored to the findings of surgical staging.^{13–15} An added benefit of staging surgery is that it also identifies those patients who do not require adjuvant treatment.¹⁷

Reviews on AEH and concurrent EC have routinely reported the rates of myometrial invasion found at the time of hysterectomy, but have not clearly defined the risk status of patients found to harbour cancer. The present study is the first in which an attempt has been made to delineate risk status for patients with concurrent EC using a recognized risk categorization scheme. Only three previous studies have provided more detailed information on the postoperative risk status of patients, but unfortunately, risk categorization was either not clear or not consistent with recent data on prognostic factors in endometrial cancer. For example, in the report of Trimble et al., the reported rate of high-risk cancers was 35%.¹⁰ However, this study classified all patients with any degree of myometrial invasion and all patients with grade 2 or 3 tumours as high risk. It has been demonstrated in a recent population-based study that five-year survival approaches 90% for patients with stage IA or IB grade 1 or 2 tumours.¹⁴ Therefore, patients with grade 2 tumours who have less than 50% myometrial invasion should be considered low risk. Application of our risk categories to the patients described in the study of Trimble et al.¹⁰ would leave 15 of 123 (12.2%) with concurrent EC identified as having significant-risk cancers.

Our finding that almost 70% of patients with concurrent EC had grade 1, low-risk disease was reassuring. However, surgical management of preoperative AEH that is limited to HBSO would result in a small proportion of patients undergoing inadequate surgery. For example, if the rate of concurrent EC is 36%, and 16% of patients with concurrent EC have significant-risk disease, six of every 100 patients with preoperative AEH managed by HBSO would have suboptimal surgery. Nevertheless, performing full staging surgery on all patients with AEH would be excessive.

Table 3. Comparison of mode of preoperative diagnosis with the proportion of patients found to have concurrent EC

Method of diagnosis	Agreement		Total
	Agreed	Upgraded	
Biopsy	24	15	39
Dilatation & curettage	21	12	33
Total	45	27	72

P = 0.58

Table 4. Determination of risk status for patients found to have concurrent EC

Grade of tumour	Stage of tumour	N	Significant risk group
1	IA	5	
	IB	12	
2	IA	1	
	IB	3	0
	IC	3	3
	IIA	1	1
Total		25	4

Therefore, cost-effective, simple methods are required to improve either the preoperative or the intraoperative identification of patients with potentially significant carcinomas. Such methods could include the use of biomarkers that identify higher risk disease, intraoperative assessment of tumour invasion, and centralized pathology review.

Centralized pathology review has improved decision making in the management of gynaecologic cancers and has also improved the accuracy of preoperative grading of endometrial cancer.^{18,19} However, this benefit of preoperative pathology reviews has not been demonstrated in the management of AEH. In the study of Trimble et al.,¹⁰ the preoperative AEH diagnosis was reviewed by a panel of three gynaecologic oncology pathologists. Consensus on the preoperative diagnosis (agreement among at least 2 of the 3 reviewers) was reached in only 39% of cases.¹⁰ A high degree of intra-observer and inter-observer variability is also found in other expert pathology review panels specifically examining the reproducibility of the AEH diagnosis.^{20–22}

Recent advances in molecular biology have led to the identification of biomarkers that can be used to allow accurate identification of high risk endometrial carcinomas preoperatively.^{23,24} Biomarkers that can assist pathologists in

Table 5. Studies of atypical endometrial hyperplasia and concurrent endometrial carcinoma

Study	Study Design	No. of Patients	Percentage with concurrent EC	Percentage of EC with myometrial invasion	Percentage of EC with SR carcinoma	Time to surgery (weeks)
Gusberg and Kaplan ³	Retrospective	18	20.0	Not recorded	Not recorded	< 8
Tavassoli and Kraus ⁴	Retrospective	48	25.0	33.3	NA	0.3–35
Kurman and Norris ⁵	Retrospective	89	17.0	46.9	NA	< 4
Janicek and Rosenshein ⁶	Retrospective	44	43.0	89.0	36.8*	7–9
Widra et al. ⁷	Retrospective	24	50.0	75.0	NA	NA
Dunton et al. ⁸	Retrospective	23	52.0	50.0	NA	NA
Shutter et al. ⁹	Retrospective	60	48.0	72.4	17.2†	< 18
Trimble et al. ¹⁰	Prospective	289	43.0	30.9	12.2‡	< 12
Current study	Retrospective	70	35.7	76	16	Mean of 11

SR: significant risk

*Two grade 1 lesions with > 50% myometrial invasion, 1 stage IIA, 2 stage IIB, 2 stage IIIA (7 of 19 cancers = 36.8%)

†Stage 1C in two cases, stage IIB in three cases (5 of 29 cancers = 17.2%)

‡13 patients with grade 1 stage IC, one patient with grade 3 stage IA, one patient with grade 3 stage IB (15 of 123 patients = 12.2%)

distinguishing between endometrial cancer, atypical endometrial hyperplasia, and benign forms of hyperplasia (simple hyperplasia and complex hyperplasia without atypia) have also been found. One example is GLUT-1, a facilitative glucose transporter found in a wide variety of cells including endometrial. This protein has been found to be overexpressed in endometrial cancers and in atypical endometrial hyperplasia, but simple and complex hyperplasia either stained weakly or showed non-staining.^{25,26} However, in patients with a preoperative diagnosis of AEH, such markers are currently unable to distinguish, between those with concurrent EC and those without.

Assessment of myometrial invasion, either preoperatively with MRI or intraoperatively through gross inspection and/or evaluation of frozen sections, can help identify patients with preoperative low grade endometrial cancers that require full staging surgery.^{27–34} Routine MRI scanning of all patients with AEH to identify those patients with deep myometrial invasion would have such a low yield that it would not be cost-effective. In our review, only 6% of patients would have benefited from such an approach. In contrast, the intraoperative inspection of the uterine cavity is simple and could easily be incorporated into the operative management of AEH. This procedure has been shown to have a sensitivity of 85% to 87% in determining the depth of myometrial invasion in patients with endometrial cancer.^{29,30} Concurrent use of frozen section analysis can further enhance intraoperative risk determination in patients

with endometrial cancer.^{31–34} However, in a review of 23 patients, only four of 11 patients found to have concurrent EC were identified by frozen section assessment.³¹

The limitations of our study arise from the relatively small number of patients and the retrospective collection of data. We did not attempt to review the effect of non-surgical treatment of AEH and the subsequent incidence of concurrent EC. However, the average age of 58 and the brief interval between the preoperative biopsy and surgery (an average of 78 days) make it unlikely that hormone treatment was utilized in this cohort. Our definition of significant risk cancer did not include patient age or lymphovascular space involvement and may have underestimated the proportion of patients with intermediate and high risk cancers.

Potential confounders in the rate of concurrent EC include patient age, BMI, method of preoperative diagnosis, and time to surgery. We found that these variables did not have a significant impact on rates of concurrent EC and the findings were consistent with those in other reports.^{6,7,9,10}

CONCLUSION

Of women with known atypical endometrial hyperplasia, 35.7% were found after surgery to have concurrent EC. Our finding that 16% of patients with concurrent EC had significant risk carcinoma supports the need for improved management of patients with preoperative AEH. Full staging surgery of all patients with preoperative AEH is not

justified; however, while awaiting the development of biomarkers that can be used to better quantify preoperative risk, intraoperative inspection of the uterus can help identify those patients requiring staging surgery.

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