ENDOMETRIAL CANCER

Practice recommendations Atypical hyperplasia, oncology consult for staging, use of estrogen after hysterectomy

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ObGyns are the first to make the diagnosis and are frequently involved in the treatment of endometrial cancer. It is the most common gynecologic cancer—more common than ovarian cancer and cervical cancer combined.

There will be an estimated 41,200 cases and 7,350 deaths from uterine cancer in 2006.

This update reviews recent studies and practice guidelines that may affect how we manage this disease.

Anticipate cancer when the diagnosis is atypical hyperplasia

Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ II, Alberts D, Curtin J. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia. Cancer. 2006;106:812–819.

When we see a diagnosis of atypical endometrial hyperplasia, we need to consider that there very well may be an endometrial cancer already present

ObGyns often manage women with a diagnosis of atypical endometrial hyperplasia, and we know that it is a precursor to endometrial cancer. A now-classic study[1] found that 29% of women with complex atypical hyperplasia go on to develop endometrial cancer, and the standard recommendation for women with complex atypical hyperplasia is hysterectomy and bilateral salpingo-oophorectomy. (The exception to surgical management is for young women who wish to retain their ability to have children; in these cases, conservative management with progesterone therapy is often attempted.)

A considerably higher rate—42.6%—of concurrent endometrial carcinoma was found, in a large NIH-sponsored study conducted by Trimble and colleagues, from the Gynecologic Oncology Group member institutions. A panel of gynecologic pathologists analyzed the diagnostic biopsy specimens and the hysterectomy slides of 289 women who had a preoperative diagnosis of complex atypical hyperplasia. Of those who had concurrent cancer, about one third of the cancers invaded the myometrium, and about 10% involved deep myometrial invasion.

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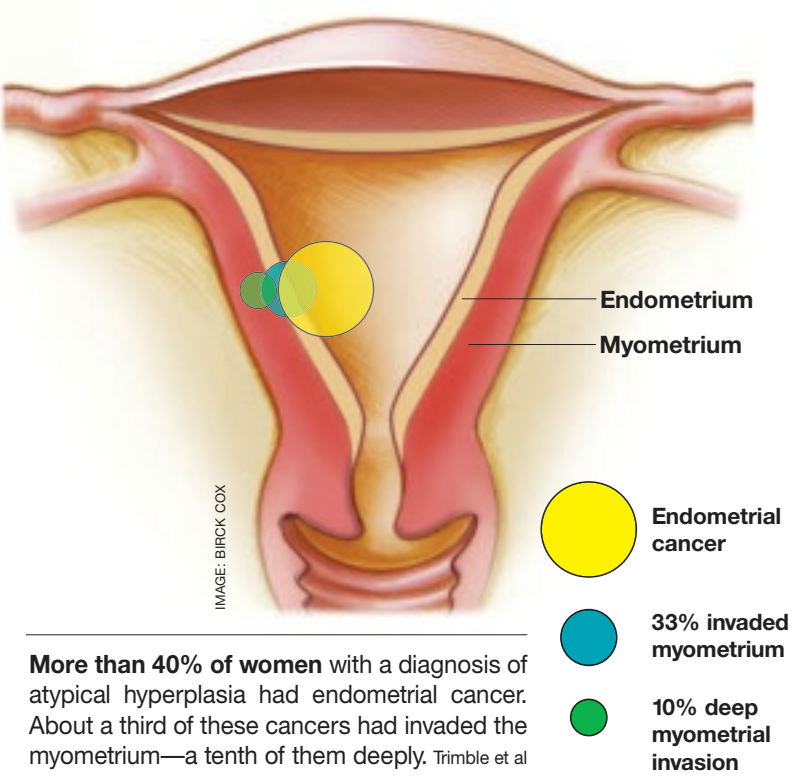
Atypical hyperplasia: A warning sign



More than 40% of women with a diagnosis of atypical hyperplasia had endometrial cancer. About a third of these cancers had invaded the myometrium—a tenth of them deeply. Trimble et al

Practice recommendations

I believe the findings of this study have two important implications for practice:

1. When taking a patient with complex atypical hyperplasia to the operating room, an intraoperative frozen section is important. Understaging can occur if the surgeon is not prepared to perform staging.
2. In counseling patients with complex atypical hyperplasia, it is important to inform them of the high risk of finding a concurrent cancer. Women who choose conservative medical management with progesterone due to their wish to retain childbearing potential should be informed of the risks. In addition, very close follow-up with serial endometrial biopsies or dilation and curettage should be considered.

REFERENCE

1. Kurman R, Kaminski P, Norris H. The behavior of endometrial hyperplasia. A long-term study of "untreated" hyperplasia in 170 patients. Cancer. 1985;56:403–411.

FAST *TRACK*

Understaging limits the oncologist's ability to select adjuvant therapy and assess risk of recurrence

No pre-op evidence of metastatic cancer? Don't get too comfortable

Orr Jr J, Chamberlain D, Kilgore L, Naumann W. ACOG Practice Bulletin Number 65. Management of endometrial cancer. Obstet Gynecol. 2005;106:413–425.

ObGyns should have a consultant gynecologic oncologist available to perform full staging in the majority of endometrial cancer cases

The most significant and controversial aspect of the new ACOG Practice Bulletin is the strong recommendation that most women with endometrial cancer undergo full staging, including pelvic washings, bilateral pelvic and para-aortic lymphadenectomy, and complete resection of all disease. The exceptions include young or perimenopausal women with grade I endometrioid adenocarcinoma associated with atypical endometrial hyperplasia, and women at increased risk of mortality secondary to comorbidities. The bulletin acknowledges that the recommendations are based on limited or inconsistent evidence (Level B).

One of the reasons for full surgical staging for most endometrial cancers is the difficulty in accurately determining grade and depth of invasion intraoperatively. Because of this difficulty, gynecologic oncologists occasionally see patients who were understaged. This limits the oncologist's ability to determine appropriate adjuvant therapy and accurately assess risk of recurrence.

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Practice recommendations

Many ObGyns feel comfortable taking a patient with complex hyperplasia or grade I endometrial cancer to the operating room if there is no evidence of metastatic disease or deep myometrial invasion. These new guidelines mean that ObGyns should have a consultant gynecologic oncologist available to perform full staging in the majority of cases of endometrial cancer.

The bulletin also offers helpful guidelines for preoperative evaluation and postoperative adjuvant treatment, and discusses specific recommendations for women found to have endometrial cancer after a hysterectomy, progesterone therapy for early grade I disease, and management of endometrial cancer in patients with morbid obesity.

Estrogen therapy after hysterectomy for early-stage endometrial cancer

Barakat RR, Bundy BN, Spirtos NM, Bell J, Mannel RS. Randomized double-blind trial of estrogen replacement therapy versus placebo in stage I or II endometrial cancer: a gynecologic oncology group study. J Clin Oncol. 2006;24:587–592.

For women with problematic symptoms that are unresponsive to other drugs, short-term estrogen may be an option. Estrogen in this setting is unlikely to significantly increase the recurrence rate of endometrial cancer

***FAST** TRACK*

Estrogen can be considered for unrelenting hot flashes and night sweats in women treated for endometrial cancer

This prospective, randomized, placebo-controlled study was initiated to examine whether estrogen replacement therapy had a deleterious effect on the risk of recurrence in patients with early-stage endometrial cancer. More than 1,236 women were randomized to either estrogen replacement therapy or placebo. Although the study did not complete accrual, and therefore definitive answers about the effect of estrogen replacement on survival cannot be made, some useful clinical information resulted.

The absolute recurrence rate in those taking estrogen therapy was 2.1%, which is quite low. This low rate did not differ significantly from the recurrence rate in the placebo group. It is unlikely that a randomized clinical trial will ever definitively answer the question of safety of estrogen replacement therapy in women with early-stage endometrial cancer. Therefore, the decision to use estrogen replacement therapy has to be individualized.

Estrogen replacement therapy will most likely be for the approximately one quarter of all women with endometrial cancer who are under the age of 50 and for whom surgical treatment of endometrial cancer will result in premature menopause.

Symptoms including hot flashes and night sweats can be addressed initially with agents such as venlafaxine, a serotonin and norepinephrine reuptake inhibitor.

For women whose problematic symptoms do not improve with these drugs, however, short-term estrogen may be an option. Estrogen in this setting was unlikely to significantly increase the recurrence rate of endometrial cancer, this study found.

Practice recommendations

The ACOG Committee Opinion for Hormone Replacement Therapy in Women Treated for Endometrial Cancer, Number 234, May 2000 (published before completion of this study) recommends individualization on the basis of potential benefit and risk to the patient.

It is a good recommendation, and now this study's results can be included, as well, in discussions with patients about risks and benefits.

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Surgery prevents Lynch syndrome cancers

Schmeler KM, Lynch HT, Chen L-M, Munsell MF, Soliman PT, Clark MB, Daniels MS, White KG, Boyd-Rogers SG, Conrad PG, Yang KY, Rubin MM, Sun CC, Slomovitz BM, Gershenson DM, Lu KH. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354:261–269.

Lu K, Broaddus R. Gynecologic cancers in HNPCC. Familial Cancer. 2005;4:249–254.

Prophylactic hysterectomy with bilateral salpingo-oophorectomy is an effective strategy for prevention of endometrial and ovarian cancer in women with the Lynch syndrome

Although ObGyns are familiar with the Hereditary Breast/Ovarian Cancer syndrome and the BRCA1 and BRCA2 genes, few are familiar with the increased risk of endometrial cancer in the Lynch syndrome, also called hereditary nonpolyposis colorectal cancer syndrome (HNPCC).

The Lynch syndrome is an inherited cancer predisposition syndrome that increases risk for endometrial cancer, colon cancer, and ovarian cancer. There are also less common cancers associated with Lynch syndrome. The genes that are responsible for inherited cancer susceptibility in families with Lynch syndrome are MLH1, MSH2, and MSH6. These genes are part of a family of genes that are responsible for repairing DNA mistakes during DNA replication. Mutations in one of the genes occur in about 1 in 1,000 individuals, which is similar in frequency to mutations in BRCA1 and BRCA2.

Women with Lynch syndrome have a 40% to 60% lifetime risk of colon cancer and a 40% to 60% risk of endometrial cancer (compare this to the 5% lifetime risk of colon cancer and 3% lifetime risk of endometrial cancer in the general population).

ObGyns can:

- Identify women who may have Lynch syndrome
- Manage their endometrial and ovarian cancer risks

The New England Journal of Medicine report helps to further define prevention strategies. Of 315 women with documented germline mutations associated with the Lynch syndrome, 61 underwent prophylactic hysterectomy and were matched with 210 women who did not undergo hysterectomy.

Key results

- None of the women who underwent prophylactic hysterectomy developed endometrial cancer, whereas 69 women in the control group (33%) developed endometrial cancer.
- None of the women who underwent bilateral salpingo-oophorectomy developed ovarian cancer, whereas 12 women in the control group (5%) developed ovarian cancer.

Practice recommendations

- These findings suggest that prophylactic hysterectomy with bilateral salpingo-oopherectomy is an effective strategy for preventing endometrial and ovarian cancer in women with the Lynch syndrome.
- For endometrial and ovarian cancer screening, the available studies have shown that measurement of the endometrial stripe is unlikely to be effective.
- Current consensus group recommendations advise an annual endometrial biopsy and a transvaginal ultrasound to examine the ovaries.
- For colon cancer screening, a colonoscopy every 1 to 2 years is recommended. ■

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In women with Lynch syndrome, lifetime risk for colon cancer and for endometrial cancer is 40% to 60%