Endometrial cancer

Prevention, detection, management, and follow up

Laurie Elit, MD, MSC, FRCSC

abstract

OBJECTIVE To review risk factors for uterine cancer; to discuss strategies for detecting uterine cancer; to outline prognostic factors and treatment; and to review the role of follow up for patients who have completed primary therapy.

QUALITY OF EVIDENCE MEDLINE was searched from January 1996 to June 1998 using the terms endometrial neoplasms, estrogen replacement therapy, hormone replacement therapy, tamoxifen, and screening. Only English language articles were reviewed. Study types included reviews. Bibliographies of articles found were searched for further relevant titles. Causation literature is available from well conducted cohort trials. Treatment recommendations are based in part on prognostic information and a few randomized controlled trials.

MAIN MESSAGE Risk factors, both intrinsic and extrinsic, are associated with uterine cancer. Family physicians have a role in preventing disease by ensuring that all women with uteri in situ using hormone replacement therapy (HRT) have progesterone therapy as part of the HRT regimen. Detection is crucial; abnormal uterine bleeding or undiagnosed postmenopausal bleeding warrants investigation with endometrial biopsy. The goal of surgery is to remove the uterus and ovaries and identify factors that make the disease at high risk of recurrence. Although adjuvant radiation therapy does not prolong survival, it does alter the pattern of disease recurrence. The goal of follow up after primary therapy is to identify recurrent disease while it is still curable.

CONCLUSIONS Family physicians play an important role in preventing uterine cancer, initiating early diagnosis of disease, and in the future, might be more actively involved in caring for patients following primary therapy.

résumé

OBJECTIF Passer en revue les facteurs de risque du cancer de l'utérus; discuter des stratégies de dépistage du cancer de l'utérus; présenter un aperçu des facteurs de pronostic et du traitement; et revoir le rôle de suivi des patientes qui ont subi une thérapie primaire.

QUALITÉ DES DONNÉES Une recension a été effectuée dans MEDLINE de janvier 1996 à juin 1998 à l'aide des termes en anglais pour néoplasmes de l'endomètre, œstrogénothérapie de remplacement, hormonothérapie de remplacement, tamoxifène et dépistage. Seuls les articles rédigés en anglais ont été retenus. Les analyses critiques ont été incluses dans les types d'études. La bibliographie des articles trouvés a été examinée pour y trouver d'autres titres pertinents. Des ouvrages sur les liens de cause à effet sont tirés d'études par cohortes bien réalisées. Les recommandations thérapeutiques se fondent en partie sur l'information pronostique et quelques essais aléatoires contrôlés.

MESSAGE PRINCIPAL Les facteurs de risque, tant intrinsèques qu'extrinsèques, sont associés au cancer de l'utérus. Les médecins de famille ont un rôle à exercer dans la prévention de la maladie en assurant que toutes les femmes qui ont toujours leur utérus et qui suivent une hormonothérapie de remplacement suivent aussi dans ce contexte une œstrogénothérapie. Le dépistage est d'importance capitale; les saignements utérins anormaux et les saignements postménopausiques non diagnostiqués méritent une investigation par biopsie de l'endomètre. Le but de la chirurgie est l'ablation de l'utérus, et des ovaires et l'identification des facteurs susceptibles de présenter des risques élevés de récurrence. Si la radiothérapie adjuvante ne prolonge pas la survie, elle modifie par ailleurs les tendances dans la récurrence de la maladie. Le suivi ultérieur à une thérapie primaire a pour but d'identifier la réapparition de la maladie alors qu'elle peut encore être guérie.

CONCLUSIONS Les médecins de famille jouent un rôle important dans la prévention du cancer de l'utérus en amorçant un diagnostic précoce de la maladie et, plus tard, en participant plus activement aux soins des patientes après une thérapie primaire.

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Cet article a fait l'objet d'une évaluation externe.

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Endometrial cancer is the most common gynecologic malignancy; 3300 Canadian women are affected annually. It ranks in incidence behind breast, bowel, and lung cancer.[1] Family physicians have an important role in preventing endometrial cancer by appropriate use of postmenopausal hormone replacement therapy (HRT). Family doctors can facilitate early diagnosis of cancer by initiating investigations or referral when abnormal bleeding occurs, especially during or after menopause. Important investigations include endometrial biopsy and possibly ultrasound.

A new role for family doctors includes ongoing follow up of patients who have undergone initial therapy for endometrial cancer. This paper aims:

- to review risk factors for uterine cancer;
- to discuss available strategies for detecting uterine cancer;
- to review briefly prognostic factors and treatment; and
- to review the role of family doctors in following up patients who have received primary therapy.

Quality of evidence

MEDLINE was searched from January 1996 to June 1998 using the terms endometrial neoplasms, estrogen replacement therapy, HRT, tamoxifen, screening, English language, and study type (including reviews). Bibliographies of articles found were searched for further relevant titles. Articles with the highest level of evidence were used as the basis for comments on each objective. Causation literature was available from well conducted cohort trials. Treatment recommendations are based in part on prognostic information and a few randomized controlled trials. Level of evidence as described by Browman et al[2] will be noted.

Risk factors for endometrial cancer. The cause of uterine cancer is unknown; however, patients present in one of two scenarios. First, if a woman has taken unopposed estrogen, cancer can arise in a hyperplastic endometrium. Second, the cancer arises in an atrophic endometrium where the carcinogen is unknown but prognosis is poorer. A woman can be at risk of endometrial cancer because of intrinsic or extrinsic factors.

Dr Elit *is a Gynecologic Oncologist and an Assistant Professor at the Hamilton Regional Cancer Centre in Ontario.* *This material was first presented at the Annual Update for Family Physicians, Obstetricians, and Gynecologists on October 21, 1998.*

Intrinsic risk factors: Intrinsic factors include factors that are a part of a woman's constitution. Onset of menarche before the age of 12 confers an increased risk of developing uterine cancer (OR = 2.6, 95% CI 1.3 - 5.0).[3] Nulliparity increases the relative risk of uterine cancer threefold. Menopause occurring after age 50 increases risk of endometrial cancer (menopause at 51 to 55, OR = 1.69, 95% CI 1.06 - 2.68; menopause between 55 and 64, OR = 3.08, 95% CI 1.71 - 5.56).[3]

Fat tissue predisposes obese women to uterine cancer by increasing unopposed estrone stimulation of the endometrial lining. Women who are 30 pounds over ideal body weight have a threefold increase in risk, and those who are 50 pounds over ideal weight have a 10-fold increased risk.[3] Lynch syndrome II includes multiple adenocarcinoma, such as familial colon cancer and a high rate of ovarian, endometrial, and breast cancer and other malignancies of the gastrointestinal and genitourinary system. Tumours of the ovary, such as granulosa cell tumours, liberate estrogen and might be associated with endometrial hyperplasia or cancer (level 3-5 evidence[2]).

Extrinsic risk factors: Extrinsic risk factors that predispose women to develop endometrial cancer involve unopposed estrogenic stimulation of the uterus. Unopposed postmenopausal estrogen replacement therapy (ERT) in women with uteri has been clearly shown to cause endometrial cancer (risk increase four to 15 times).[2] We continue to see patients receiving unopposed ERT, and typically they are women who have taken ERT for a long period with continual renewing of prescriptions and little or no gynecologic assessment.

Often, cervical cancer patients who have become menopausal as a result of external beam radiation present with enlarged uteri, as they have been inappropriately prescribed ERT only. Hormone replacement therapy for women with uteri in place must include addition of either cyclic or continual progesterone that will cause a medical slough of the hyperplastic endometrium. Adding progesterone to ERT appears to decrease the rate of uterine cancer to that of the general population.[4] As a result, patients taking HRT need investigations only when bleeding occurs at unexpected times. If bleeding occurs at any time other than the expected time for withdrawal bleeding in patients on a cyclic schedule of estrogen and progesterone, patients require an endometrial aspirate. If bleeding occurs at any time after the first 9 to 12 months in patients taking continuous combined estrogen and progesterone, patients should have an endometrial aspirate (level 3-5 evidence).

Tamoxifen and endometrial cancer: Killackey and associates[5] first reported an association between uterine cancer and tamoxifen in women who were using the drug to prevent recurrent breast cancer. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B14 randomized controlled trial (RCT) addressed the benefits of tamoxifen versus placebo in estrogen-receptor positive and node-negative breast cancer patients.[6] Approximately 2843 women participated in this trial.

Endometrial polyps occurred in 36% of the tamoxifen patients and 10% of the placebo group. The rate of endometrial cancer was 7.5-fold higher in the tamoxifen group (level 1 evidence). Most of the endometrial cancers (88%) were stage 1 and 78% were low-grade lesions. The rate of uterine cancer was 0.2/1000 in the placebo group and 1.6/1000 in the tamoxifen group. The cumulative rate of breast cancer relapses was reduced from 227.8/1000 in the placebo group to 123.5/1000 in the tamoxifen group. Results of this trial showed that tamoxifen increases the risk and morbidity associated with endometrial cancer, but that the beneficial effects of tamoxifen for preventing recurrent breast cancer far outweighed the risk of endometrial cancer.

So how should we monitor the gynecologic health of a patient receiving tamoxifen? Barakat and colleagues[3] prospectively attempted endometrial aspiration for 126 women taking tamoxifen: 4.8% of aspirations were unsuccessful due to cervical stenosis, 5.8% of patients were noncompliant, 4% of samples were abnormal, and an additional 6% of patients had to undergo dilation and curettage for abnormal bleeding. Given that the annual risk of endometrial cancer is 2 to 3 in 1000, and given that it was difficult to obtain samples in 10% of women and that abnormal histology was usually associated with abnormal vaginal bleeding, annual screening for asymptomatic women is not supported (level 5 evidence).

Diagnosis of endometrial cancer. There are many ways to obtain supporting evidence for endometrial cancer. For example, a Pap smear showing adenocarcinoma cells likely of uterine origin mandates further investigation. A thickened endometrial echo on a transvaginal ultrasound also warrants further assessment.[7] Kedar and coworkers[8] showed that an endometrial stripe greater than or equal to 8 mm is associated with atypical hyperplasia or polyps. Lahti and associates showed that, if endometrial thickness is 5 mm or greater in postmenopausal women, 51.2% will have normal results but no abnormal results will be missed (level 5 evidence).[7,9]

Definitive diagnosis of endometrial cancer is made only by endometrial biopsy. Initially, this should be conducted in the office using one of many endometrial aspiration devices (such as the Pipelle or Vabra). Family doctors or gynecologists can do office endometrial aspirations (sensitivity 67%, specificity 99%, positive predictive value 93%, negative predictive value 96%[10]). In circumstances where ultrasound shows thickened endometrium and biopsy is not diagnostic or where endometrial aspiration cannot be completed, patients should undergo dilation and curettage under general anesthesia. Hysteroscopic assessment of the uterus can help to identify the area of abnormality and to obtain directed biopsies.

Once patients have been diagnosed as having endometrial cancer, they should be assessed by either a gynecologist or a gynecologic oncologist. A gynecologic oncologist should be involved if a patient has advanced cancer or if there is a serous or clear cell cancer.

Management of endometrial carcinoma

Prognostic factors: Seventy-five percent of all patients with uterine cancer have stage 1 disease (cancer confined to the uterus), so this discussion of prognostic factors will be limited to this setting. The literature on poor prognostic factors is difficult to interpret because the outcome variable of interest is survival but most authors use surrogate end points like risk of recurrent disease or positive nodal status at time of diagnosis.

Malkasian et al[3] showed that, as age increases, so does risk of disease recurrence (17.5% of women older than 60 had recurrences compared with 8.5% of women younger than 60). The FIGO (International Federation of Gynecologists and Obstetricians) staging system before 1988 was clinical, and stage 1 uterine cancer was subdivided on the basis of uterine length being greater or less than 8 cm. The poor prognosis of large uterine size was reflected in the higher rate of positive pelvic nodes (12% vs 8%) and positive para-aortic nodes (7% vs 3%). The FIGO system now uses surgical staging, which subdivides stage 1 on the basis of depth of myometrial invasion. Multivariate analysis has shown that myometrial invasion is the strongest predictive factor for recurrent disease. Depth of tumour penetration into the myometrium is associated with nodal spread of disease.

Histologies that, regardless of grade, have an unfavourable prognosis are adenosquamous, serous,

and clear cell adenocarcinoma. Adenosquamous and clear-cell cancers have a propensity to spread to nodes early in the course of disease. Serous cancer has a propensity to involve peritoneal surfaces, so initial surgery warrants staging as in ovarian cancer; this includes an omentectomy and multiple peritoneal biopsies to ensure there is no microscopic upper abdominal disease.

Increasing grade is associated with greater depth of invasion and an increased risk of positive nodal disease. Grade 1 is defined as highly differentiated adenomatous carcinoma. Grade 2 is defined as moderately differentiated adenomatous carcinoma with partly solid areas. Grade 3 is defined as predominantly solid or entirely undifferentiated carcinoma. Patients with stage 1 disease who had vascular space involvement (VSI) account for 26.7% of deaths; those without VSI account for 9.1% ($P < .01$).[11] Positive peritoneal cytology accounts for 14% of deaths compared with negative cytology, which accounts for 9.7%.[12] Presence of estrogen or progesterone receptors correlates with lower grade and thus better prognostic disease.[3]

Prognostic factors that account for most of the treatment failures are grade and depth of invasion (level 5 evidence).

Surgical therapy for endometrial cancer: Endometrial cancer is treated initially by a surgical procedure that is completed through a vertical incision, and washings are taken on entry into the peritoneal cavity. To rule out metastasis, thorough exploration of the abdomen, assessing the peritoneal surfaces, liver, spleen, kidneys, bowel, bladder, and pelvic and para-aortic nodes, is required. The uterus, cervix, fallopian tubes, and ovaries are removed. An RCT is being conducted through the Gynecologic Oncology Group (LAP2 or GOG 9301) to evaluate whether the same staging and histologic information can be obtained by laparoscopy[13] (level 1-2 evidence).

Adjuvant therapy: A decision to offer adjuvant therapy is usually based on risk of vaginal or pelvic recurrence, and the surrogate end point here again is risk of nodal disease. Although it is well accepted that adjuvant pelvic radiotherapy does not improve survival, it does affect the pattern of recurrence. For example, if a patient develops recurrent disease at the apex of her vagina, the necrotic tumour can cause incessant foul vaginal discharge or bleeding. Although we do not yet have treatment that can alter the risk of dying from recurrent disease, if a patient is at high risk of developing pelvic disease, use of adjuvant pelvic radiation will decrease the likelihood of developing a central pelvic recurrence.

Morrow and colleagues[12] defined low-risk patients as those with stage 1 grade 1 or 2 disease confined to the endometrium; these patients received no further treatment and developed no recurrent disease. Patients at high risk for nodal involvement are those with grade 3 disease, especially if the depth of invasion involves more than half of the myometrium. Radiation can minimize risk of recurrent pelvic disease. Even when pelvic nodes are positive, Morrow and co-workers[12] showed that with pelvic radiation, 72% of women are alive at 5 years. Intermediate-risk patients include those with grade 3 disease and inner half myometrial involvement, or those with grade 1 and 2 inner or outer half disease. Adjuvant radiation therapy does not appear to affect survival in this group of women. Radiation does improve local regional control. The Gynecologic Oncology Group 99 showed that pelvic failure with radiation was about 2% and without radiation about 12% (level 1 evidence).[14] Some patients with vault relapses were salvaged with radiation.

Table 1. **Studies on the outcome of follow up for patients with uterine cancer**

STUDY	CASES OF UTERINE CANCER	RECURRENCE	DIAGNOSIS METHOD	
			CLINICAL	LABORATORY: ROUTINE FOLLOW UP
Shumsky et al[16]	435	53	GP 34 (75%)	11 (21%)
Berchuk et al[15]	354	44 (12%)	Symptoms (84%)	No data
Agboola et al[17]	432	50 (11.6%)	No data	No data

Follow up after initial treatment. Two questions concerning follow up must be addressed. First, must patients with stage 1 endometrial cancer be followed up after hysterectomy? Three case series have addressed this subject. Follow up must have a purpose; if a patient can be cured when the cancer recurs, then it makes sense to be vigilant (**Table 1**[15-17]).

Berchuk and associates[15] showed that, in 44 patients with recurrent disease, only eight survived. Six of these patients had a vault recurrence. Thus, if follow up helps identify vault recurrences, it is advantageous. Shumsky and colleagues[16] showed that there was no statistical difference in survival between the group detected on routine follow up and those who were detected when they developed symptoms. Shumsky et al[16] also showed that vault cytology was not diagnostic in any patient. Agboola and co-workers[17] and Berchuk and co-workers[15] both show

no difference in survival between patients who present with and without symptoms. Thus, the role of routine follow up is in question (level 5 evidence). To determine the role of follow up, a well designed RCT needs to be conducted.

The second purpose of follow up involves dealing with other ramifications of the diagnosis of cancer and its treatment, such as sexual dysfunction or psychological distress. Which health care specialist is best able to deal with these issues (ie, gynecologic oncologist, gynecologist, family doctor, or nurse practitioner) again is unclear. At present, women with low-grade stage 1 disease at the Hamilton Regional Cancer Centre are given the option of follow up by their family physicians, gynecologists, or cancer physicians. Follow up should include discussion of symptoms and a physical examination including inspection of the vagina and a pelvic and pelvi-rectal examination. Given the limitations of health care resources, the tradition of surveillance every 3 months for 5 years of all women treated for uterine cancer through the local cancer centre has been challenged, and alternative patterns of care need to be considered.

Conclusion

Family physicians have an important role in preventing uterine cancer with appropriate use of combination replacement therapy in women who still have uteri. An office endometrial sample or appropriate referral for this procedure is important in making an early diagnosis of malignancy. The importance of follow up for women who have had a diagnosis of uterine cancer remains to be determined. Consensus on which health care professionals are considered appropriate to conduct this follow up is definitely shifting toward family practitioners.

Correspondence to: *Dr Laurie Elit, Hamilton Regional Cancer Centre, Division of Gynecologic Oncology, 699 Concession St, Hamilton, ON L8V 5C2; telephone (905) 389-5688; fax (905) 575-6317; e-mail* laurie.elit@hrcc.on.ca

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Key points

- Unopposed estrogen is a known risk factor for endometrial cancer. Progesterone must always be added to estrogen for women with uteri.
- Tamoxifen used to prevent recurrent breast cancer increases the risk of endometrial cancer, but the benefits of tamoxifen far outweigh the risks.
- Poor prognostic factors include increasing age, large uterus, myometrial invasion, certain cell histologies, vascular space involvement, peritoneal cytology, and absence of estrogen or progesterone receptors.
- Treatment is surgical: total hysterectomy and oophorectomy and assessment of nodes. Adjuvant radiation therapy does not alter the risk of dying, but reduces central pelvic recurrence.
- Evidence to date does not indicate the best type of follow-up assessment: regular assessment versus presentation for symptoms.

Points de repère

- L'œstrogène sans opposition est un facteur de risque connu du cancer de l'endomètre. La progestérone doit toujours être ajoutée à l'œstrogène chez les femmes qui ont leur utérus.
- Le tamoxifène utilisé dans la prévention de la récurrence du cancer du sein augmente le risque de cancer de l'endomètre, mais les avantages du tamoxifène dépassent largement ses risques.
- Au nombre des facteurs de pronostic défavorables figurent l'avancement en âge, un utérus de grande taille, une invasion myométriale, certains résultats histologiques, l'entrée en cause de l'espace vasculaire, la cytologie péritonéale et l'absence de récepteurs d'œstrogène et de progestérone.
- Le traitement est de nature chirurgicale: l'hystérectomie complète et l'ovariectomie ainsi que l'évaluation des nodules. La radiothérapie adjuvante n'influence pas le risque de décès, mais réduit la récurrence au niveau pelvien central.
- Les données probantes disponibles à ce jour n'indiquent pas le meilleur type d'évaluation de suivi: une évaluation régulière ou l'apparition de symptômes.

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