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Clinical Aspects of Risk in Women With Endometrial Carcinoma

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Abstract Carcinoma of the endometrium is the most common gynecologic malignancy, expected to account for 33,000 new cases and 6,000 deaths in 1995. Most endometrial cancers occur in postmenopausal women and produce abnormal vaginal bleeding. Some women exhibit the premalignant changes of atypical endometrial hyperplasia before developing an overt carcinoma. Identified epidemiologic risk factors include obesity, diabetes mellitus, use of unopposed exogenous estrogens, estrogen-secreting tumors, and a reproductive history characterized by prolonged estrogenic predominance. Diagnosis can be readily established by outpatient endometrial biopsy. Because clinical estimates of disease extent and spread are subject to substantial error, endometrial cancer is now a surgically staged neoplasm. A well-defined set of surgicopathologic risk factors have been incorporated into the staging scheme. Women with extrauterine disease comprise about 20% of cases and are at greatest risk for tumor recurrence and death from disease. Within the much larger group of women whose tumors are limited to the uterus, recurrence risk can be stratified by cytologic grade, cell type, depth of myometrial invasion, and extension to the cervix. About two-thirds of women have low-risk disease confined to the uterus when these criteria are employed, while the remaining one-third have high-risk subtypes. Recent areas of investigation have focused on molecular and genetic markers. Two clinical observations currently being examined are the poorer survival of Black women with uterine cancer and the apparent association of endometrial lesions with chronic tamoxifen suppression in women with breast carcinomas.

Key words: Clinical features, endometrial carcinoma, risk assessment

CLINICAL SYNOPSIS

Endometrial carcinoma is the most common gynecologic malignancy and the fourth most common cancer among women. Estimates for 1995 suggest that this neoplasm will be newly diagnosed in 33,000 women and will account for 6,000 cancer deaths [1]. Endometrial cancer is more common in the perimenopausal and postmenopausal age groups, with most large series reporting an average age at diagnosis of about 60 years [2].

Epidemiologic risk factors are well recognized and can usually be connected to a clinical setting of chronic, unopposed estrogenic stimulation of the endometrial lining. Included in this group are women with a history of long-term estrogen use, those who have estrogen-secreting tumors, and those with infrequent ovulation, low parity, or late menopause. Obesity has been associated

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with an increased risk of endometrial cancer, presumably related to peripheral conversion of adrenal steroids to estrone by adipocytes. Diabetes mellitus has also been identified as an independent risk factor.

Endometrial cancers that develop within the context of estrogenic dominance tend to be well-differentiated and steroid hormone receptor-positive [3]. Some of these hormonally associated cancers develop from hyperplastic precursor lesions. Precursor lesions with significant potential for malignant transformation are termed atypical adenomatous hyperplasias and are characterized by an increase in gland number and complexity (architectural atypia), as well as nuclear pleomorphism and increased epithelial proliferative activity (cytologic atypia). About one-third of untreated atypical hyperplasias will progress to endometrial carcinomas over a period of 5–10 years [4].

Virtually all women with endometrial cancer have abnormal vaginal bleeding. In most situations, the patient promptly seeks medical advice and evaluation for such episodes. Office endometrial biopsy is the diagnostic procedure of choice for women with suspected endometrial cancer [5]. A biopsy technique that uses multiple passes of the biopsy instrument will provide adequate tissue for diagnosis in most cases [6]. Operative dilatation and curettage or hysteroscopy with biopsy may be required in unusual situations where outpatient biopsy is inadequate or technically impossible to perform.

Surgical Staging: Histopathologic Risk Factors

The clinical determination of disease extent and spread in women with endometrial cancer is difficult. Tumors metastasize by direct extension within the pelvis, by lymphatic spread to pelvic and paraaortic lymph nodes, and by hematogenous dissemination to more distant sites. Because clinical staging produces an incorrect assessment of disease spread in one-third of patients [7,8], endometrial cancer is now staged surgically (Table I). About 80% of cases are surgical Stages I or II.

Histopathologic prognostic factors have been identified by a careful assessment of extensive

TABLE I. Surgical Staging of Uterine Fundal Tumors—FIGO 1988

Stage	**I**	**Tumor limited to the uterine fundus**
	IA	No myometrial invasion
	IB	Myometrial invasion ≤ 50%
	IC	Myometrial invasion > 50%
Stage	**II**	**Tumor extention to the cervix**
	IIA	Superficial glandular spread
	IIB	Stromal invasion
Stage	**III**	**Regional tumor spread**
	IIIA	Involvement of uterine serosa, adnexa, or positive peritoneal cytology
	IIIB	Vaginal metastases
	IIIC	Pelvic or paraaortic lymph node metastases
Stage	**IV**	**Advanced pelvic disease or distant spread**
	IVA	Mucosal invasion of bladder/rectum
	IVB	Distant metastases

surgical biopsy data obtained at the time of hysterectomy and staging laparotomy [9,10]. These risk factors can be conveniently categorized into uterine and extrauterine groups. Uterine factors associated with a greater risk of recurrence and poor prognosis include high tumor grade, presence of a variant cell type, such as papillary serous or clear cell carcinoma, extension to the cervix, depth of invasion into the myometrial wall, and the presence of lymph-vascular space invasion. In contrast to women with grade 1 tumors, those with high grade or variant cell type tumors tend not to fit the risk profile associated with chronic estrogenic stimulation. They tend to be older and less obese than the "typical" patient, and they generally do not have a long history of exogenous estrogen usage [11–13]. As expected, the presence of extrauterine disease conveys a poorer prognosis. Common areas of metastasis include the peritoneal surfaces, omentum, pelvic or paraaortic lymph nodes, fallopian tube or ovary, and distant sites such as liver, lung, or bone.

The Gynecologic Oncology Group's staging study provides a detailed analysis of histopathologic risk factors in 895 evaluable patients [10]. For patients without extrauterine disease, those with grade 3 tumors had the greatest incidence of tumor recurrence. For those with documented extrauterine spread, intraperitoneal disease, aortic node metastases, or multiple site involvement had the poorest prognosis. Relative risk data from this study are summarized in Table II.

Treatment of Advanced or Recurrent Disease

Although women with grade 1 adenocarcinomas confined to the uterus have excellent survival rates following hysterectomy, those with advanced or recurrent endometrial cancer generally die with progressive disease. Rare patients who develop isolated vaginal cuff recurrence and a few patients with nodal metastases can be cured by radiotherapy [14,15]. About 25% of patients with metastases have objective responses to progestational therapy [16]. A number of cytotoxic agents—including cisplatin, carboplatin, doxorubicin and taxol—also have demonstrated activity in patients with advanced disease [17–20]. Response rates of 30–40% have been typically reported. Unfortunately, responses to systemic therapy tend to be short-lived; long-term survival is uncommon. Efforts to improve survival outcome by employing postoperative therapy in an adjuvant setting have been evaluated in several prospective trials [21–24]. No statistically significant advantage for adjuvant pelvic irradiation, progestational agents, or chemotherapy has been demonstrated.

MOLECULAR AND GENETIC FACTORS

Several recent investigations have evaluated the prognostic potential of non-histopathologic markers in endometrial tumors. Preliminary data for DNA ploidy, S-phase fraction, AgNOR, oncogenes, and tumor suppressor genes have been developed largely from archival material [25–28]. The clinical implications of these findings are *not* yet clear. It seems likely that routine prospective assessment of these features will provide an additional level of information which might prove useful in predicting recurrence risk.

Clinical observations would also suggest that some women have a genetic predisposition to develop endometrial carcinoma. Endometrial tumors have been identified as a component of some cancer family syndromes [29]. Although the individual risk of developing cancer approaches 50% for female members of such families, the total number of cancers is small. Women with a history of breast, colon or ovarian cancer are also at increased risk for endometrial cancer, suggesting a genetic link among these adenocarcinomas. Second primary neoplasms may occur eight or more years after the initial diagnosis [unpublished results].

POTENTIAL TARGET POPULATIONS FOR CHEMOPREVENTION

Chemopreventive therapy should probably not be considered for across-the-board treatment of postmenopausal women. Nevertheless, several subpopulations of women may be appropriate candidates for further evaluation based upon epidemiologic and historical factors. These groups might include women with biopsy-proven adenomatous hyperplasia, obese postmenopausal women, women with a family history of endometrial carcinoma or a personal history of breast, colon or ovarian cancer, and diabetics. Unfortunately, current knowledge cannot identify a subgroup at risk for future

TABLE II. The Proportional Hazards Modeling of Recurrence-Free Interval

Variable	Regression coefficient	Relative risk	Significance test[a] (p value)
Among patients *with* metastases[b]			
Number of metastatic sites present			
1	2.50	12.0	
2	2.88	18.0	15.1 (0.002)
3, 4	3.81	45.0	
Additional factors that contribute to risk			
Deep myometrial invasion	1.57	4.8	
Grade 2,3—adenocarcinoma	0.719	2.1	
Grade 3—adenosquamous carcinoma	0.595	1.8	
Positive washings	0.528	1.7	
Among patients *without* metastases			
Adenocarcinoma			
Grade 1	1.54	4.7	
Grade 2	1.93	6.9	25.8 (< 0.0001)
Grade 3	2.10	15.0	
Adenosquamous carcinoma			
Grade 1	0.0	1.0	
Grade 2	1.34	3.8	6.73 (0.08)
Grade 3	2.10	8.1	
Adenoacanthoma			
Grade 1–3	0.0	1.0	
Among patients *without* metastases[b]			
Myometrial invasion			
Endometrium only	0.000	1.0	
Superficial	1.39	4.0	
Middle	1.33	3.8	11.9 (0.02)
Deep	1.53	4.6	
Age	–0.0236	–	Z = –0.230 (0.8)*
Age^2	0.000339	–	Z = 0.417 (0.7)
45 (arbitrary reference)	0.000	1.0	
55	0.134	1.1	
65	0.332	1.4	
75	0.593	1.8	
Vascular space involvement	0.896	2.4	8.01 (0.005)
Positive washings	0.865	2.4	9.67 (0.02)
Isthmus/cervix involvement	0.474	1.6	3.67 (0.06)
Radiation therapy			
Brachytherapy only	–0.974	0.38	
External beam	0.102	1.1	5.69 (0.06)

[a] Likelihood ratio test unless otherwise stated, [b] Metastatic sites: paraaortic nodes, pelvic nodes, adnexal spread, gross laparotomy findings, * p = 0.07 without the second-degree term (*i.e.*, age^2).

development of a poor prognosis endometrial carcinoma—papillary serous, clear cell, or grade 3 lesions.

Recent clinical reviews have noted a poorer prognosis for Black women with endometrial carcinoma compared to white women, even when controlled for stage and other risk factors [30]. If the reasons for this survival difference can be further delineated, some postmenopausal Black women might be considered for preventive trials. Similarly, if a more refined understanding of the association between tamoxifen use and endometrial lesions can be developed [31,32], breast cancer patients receiving long-term hormonal suppression might also be targeted for study.

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