

Symptoms, signs and clinico-pathological prognostic factors

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Abstract. — *The symptoms and signs of endometrial cancer are described when postmenopausal bleeding is dominant. The conventional (clinico-pathological) prognostic factors are analysed and new molecular markers summarised. These prognostic indices should contribute to the assessment of tumour biology, determine patient risk status and assist in treatment planning for the individual patient. Given their relevance, patient age and race, the stage of the disease, its histological grade and type, myometrial invasion, cervical involvement, and lymph node metastases deserve to be mentioned.*

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Introduction

Carcinoma of the endometrium is the most common female genital tract malignancy in developed countries, representing approximately 34,000 new cases and 6,000 deaths annually in the United States [27]. This cancer is the fourth most common cancer in women, ranking beneath breast, lung and colon cancers. However, in developing countries, where screening programmes are not available, cervical cancer remains the major cause of cancer mortality.

Endometrial cancer is a disease that occurs primarily in postmenopausal women in their sixth and seventh decades at an average age of 62 years. Eighty-five to 90% of cancers occur in women over 50 years of age and this malignancy is increasingly aggressive with advancing age.

Clinical features

■ Symptoms and signs

Most patients afflicted by endometrial cancer present early in the development of the disease with easily recognisable symptoms which will mandate an adequate diagnostic evaluation. The main symptoms of endometrial cancer are irregular bleeding and/or discharge occurring in a peri- or postmenopausal woman. However, the causes of such bleeding may be non-genital, genital, extra-uterine or uterine. Non-genital tract sites should be considered based on patient history and examination. Invasive tumours of the cervix, vulva, and vagina are evident on examination and should undergo biopsy if present. Traumatic bleeding from an atrophic vagina may also account for up to 10% of all causes of postmenopausal bleeding.

The prominent symptom characteristic of endometrial cancer is postmenopausal bleeding. Approximately 85% of cases occur in this group, and in about 90% of them the initial complaint is genital bleeding.

In a few patients with endometrial cancer, especially in older patients, bleeding may not occur because of cervical stenosis. These women may complain of pelvic discomfort due to uterine enlargement and eventual associated infection. The pain may be referred to the hypogastrum or to both iliac fossae, tends to be cyclic, colic in type, and is probably caused by expulsive uterine contractions. Pain may also be a late symptom associated with metastatic disease. It is rare, but the initial symptoms of endometrial cancer may be a purulent, offensive vaginal discharge: pyometra; watery discharge: hydrorrhoea; or a blood-tinged discharge: haematometra. These findings are often associated with a poor prognosis since there is a diagnostic delay [32].

Fortunately, only 7 to 10% of postmenopausal uterine bleeding is due to endometrial cancer [12, 16, 20]. Endometrial atrophy is the most common finding, accounting for 60 to 80% of postmenopausal haemorrhage. Other possible causes of bleeding in this age group include hormone replacement therapy, endometrial hyperplasia and endometrial polyps (table 1). However, a thorough investigation should be undertaken to exclude cancer: transvaginal ultrasound examination, preferably with colour Doppler, may be an adjunct of the indispensable endometrial sampling (obtained by aspiration biopsy, or hysteroscopy with biopsy, or dilatation and curettage) for evaluating the uterine cavity and to select patients for additional testing. Common errors include assuming the bleeding is due to hormonal therapy, atrophic vaginitis, or that the haemorrhage is

Table I. Causes of postmenopausal uterine bleeding

Cause of bleeding	Frequency (%)
Endometrial atrophy	60-80
Hormone replacement therapy	15-25
Endometrial hyperplasia	5-15
Endometrial polyps	2-12
Endometrial cancer	7-10

too scanty or non-persistent to warrant investigation. It is known that the amount of bleeding does not correlate to its seriousness. A single episode of spotting has the same chance of being caused by endometrial cancer as 2 to 6 days of bleeding in a postmenopausal woman [16]. Furthermore, the same authors have shown that the older the patient with bleeding, the greater the risk of cancer. This risk of developing endometrial cancer has even been quantified: 9% for 50, 16% for 60, 28% for 70, and 60% for 80 year-old women [28].

Premenopausal women with endometrial carcinoma generally also complain of abnormal uterine bleeding; this is often characterised as metrorrhagia, less often as menometrorrhagia. Younger patients, under 40 years, with persistent or recurrent abnormal bleeding should also have endometrial evaluation to exclude this malignancy, since about 2 to 4% of endometrial cancers occur in this age group.

Endometrial cancer may also be diagnosed (1 to 5% of cases) in an asymptomatic woman. This may result from investigation of an abnormal Pap smear, discovery of cancer in an uterus removed for a benign gynaecological condition, or evaluation of an abnormal finding on a pelvic ultrasound or other imaging technique obtained for unrelated reasons. Women who are found to have endometrial malignant cells on a Pap smear generally have a more advanced stage of the disease [11].

■ Physical examination

The general physical examination of the patient with endometrial cancer is frequently normal. However, obesity and hypertension as well as diabetes are commonly associated factors. Rarely, supraclavicular or inguinal lymph node metastases may be detected. The abdominal examination is usually normal, except in advanced cases in which ascites or abdominal masses may be present. The vulva, vagina and cervix should be carefully inspected and palpated to look for metastases. This examination is generally normal. On bimanual examination the uterus is usually small. It can, however, be enlarged by the tumour or by pyo-haematometra or fibroids. In advanced cases, the uterus may not only be enlarged, but also fixed and irregular in shape. The adnexa should also be evaluated for masses. Finally, the bimanual rectovaginal examination should evaluate the parametria and the cul-de-sac for nodularity or induration.

Prognostic factors

In general, the prognosis for most patients with endometrial carcinoma is relatively good with an overall 5 year survival rate of 73.4% (FIGO's Annual Report, vol. 23, 1998). This is in contrast to many other cancers, including gynaecological malignancies. The main reason for this is related to the early symptoms of postmenopausal or intermenstrual bleeding which lead women to seek medical consultation soon after the

Table II. Prognostic factors in endometrial carcinoma

Age, race	Cervical extension
Stage of disease	Intraperitoneal tumour
Histological type	Adnexal metastasis
Histological grade	Peritoneal cytology
Myometrial invasion	Hormonal receptors
Lymph-vascular space invasion	DNA ploidy/proliferative indices
Lymph node metastasis	Oncogene amplification or mutation
Tumour size	Tumour suppressor gene mutation

first episode. Moreover, this tumour is generally contained for long periods of time by the myometrium, and spreads late to the lymph nodes. It is therefore not surprising that approximately 73% of patients with endometrial cancer present with stage I disease. However, endometrial carcinoma is a heterogeneous disease. Hence, clinical, histological, and more recently, molecular prognostic factors have been studied to help determine the biological characteristics of the tumour and predict the clinical course of the disease. Furthermore, the prognostic determinants are also used as selection criteria for patients most likely to benefit from adjuvant therapy. This knowledge should allow clinicians to individualise treatment, sparing the low-risk subsets of patients unnecessary complementary therapy, and assigning treatment without delay to the high-risk groups, because they have an increased risk of developing recurrences. Unfortunately, to date, it still has to be proven that identification and application of the prognostic indices improve survival of the high-risk patient. The prognostic variables, which strongly correlate to each other, are presented in Table II.

■ Patient age, constitution and race

Younger women with endometrial carcinoma tend to have a better prognosis than older women. For instance, the analysis of 3,839 patients with surgical stage I endometrial carcinoma showed that 30 to 39 year-old women had a 5 year survival of 97.1%, which decreased to 72.9% among 70 to 79 year olds, and 56.5% in those over 80. Correlating age and survival, similar trends were also noted for stages II, III and IV (FIGO's Annual Report, vol. 23, 1998). Decreased survival is associated with deep myometrial invasion and increased risk of extra-uterine spread for the different age groups^[21]. This study also showed that none of the patients under 50 years of age developed recurrent cancer, compared to 12% of patients aged 50 to 75 years and 33% of those over 75.

Data have accumulated to suggest that there are at least two pathogenic types of endometrial cancer. The most common type arises in younger, obese women with a history of hyperoestrogenism (anovulatory uterine bleeding, infertility) and coexisting endometrial hyperplasia. The second type of cancer tends to occur in older, slender women, and is not associated with endometrial hyperplasia. On the contrary, it generally arises adjacent to atrophic endometrium. Younger patients tend to have better differentiated tumours (grade 1 or 2), superficial invasion of the myometrium, high levels of oestrogen and progesterone receptors, and a favourable prognosis. The second group of patients with a poor prognosis tends to have grade 3 tumours, deep myometrial invasion, lymph node metastasis, and low sensitivity to progestagens^[4].

Diabetes mellitus and hypertension are frequently associated with endometrial cancer; this is of prognostic importance because they may influence treatment.

Although more prevalent in white than black women, endometrial carcinoma has a considerably worse prognosis and diminished survival in the black population. A

recent report on 372 surgically staged and uniformly treated patients showed that black women had a significantly worse 5 year disease-free survival (52.8%) than white women (75.2%)^[6]. High tumour grade, deep myometrial invasion, lymph node metastasis, and malignant cells in peritoneal cytology are all significantly more frequent in black women with endometrial cancer than in white patients. Even after controlling for clinico-pathological and socio-economical factors, race remained a significant prognostic parameter^[3,6].

■ Stage of disease

The stage of endometrial carcinoma is considered to be the single most significant prognostic factor affecting survival. However, a review on 1,566 patients with endometrial carcinoma showed that in those patients surgically staged, survival related more strongly to depth of myometrial invasion than stage of disease^[33]. However, as consistently demonstrated by numerous studies, survival is strongly and significantly correlated to the stage of disease. For instance, the same review showed that 81% of patients were allocated to stage I, 11% to stage II, 6% to stage III, and only 2% to stage IV. The corresponding 5 year survival rates were 83%, 73%, 52%, and 27% respectively^[33]. The FIGO's 23rd Annual Report (1998) analysing 7,350 surgically staged endometrial carcinomas refers to frequencies of 72.8% for stage I, 10.9% for stage II, 13.1% for stage III, and 3.2% for stage IV. The corresponding 5 year survival rates are 87%, 72%, 51%, and 9% respectively.

■ Histological type

Non-endometrioid histological subtypes account for approximately 10% of endometrial cancers and have an increased risk of local recurrences and distant metastases^[34]. Non-endometrioid types include: mucinous, papillary serous, clear cell, and the rare squamous, undifferentiated and mixed carcinomas. The overall survival for patients with one of these more aggressive subtypes was 33% in comparison to 92% among patients with endometrioid tumours^[34].

Endometrioid carcinomas include two major variants: adenoacanthoma, also called "adenocarcinoma with squamous metaplasia", and adenosquamous carcinoma when both the glandular and the squamous components are malignant. Recent studies have shown that adenoacanthoma has the same prognosis as its pure counterpart. For adenosquamous carcinomas, it is probable that the degree of differentiation of the adenocarcinoma is responsible for the final prognosis and not the squamous component per se. No difference in the 5 year survival rate for the two pathological entities has been demonstrated when evaluated by tumour grade^[23].

■ Histological grade

Tumour differentiation (grade) has strong prognostic implications and is one of the most sensitive indicators of survival. It has been found that recurrences developed in 7.7% of grade 1 endometrial tumours, 10.5% of grade 2, and 36.1% of grade 3 tumours. The rates for patients with grade 1 and 2 tumours were 92% and 86% respectively for 5 year disease-free survival, in contrast to 64% for patients with grade 3 tumours^[22]. Other groups reported similar results studying clinical stage I endometrial cancers^[10]. Significantly, increasing tumour grade correlates with deep myometrial invasion, cervical extension, and lymph node metastases.

■ Myometrial invasion

Increasing depth of invasion is associated with an increasing likelihood of grade 3 tumours, extra-uterine spread, lymph node metastases, recurrences, and decreased survival, since access to the lymphatic system increases as cancer progressively invades the myometrium^[5]. Myometrial invasion is therefore an essential prognostic parameter. Only 1% of patients without demonstrable myometrial invasion had pelvic lymph node metastases, compared to patients with outer one-third myometrial invasion who had 25% pelvic and 17% aortic lymph node metastases. Different studies have shown that patients with non-invasive or superficially invasive tumours have an 80% to 90% 5 year survival rate, in comparison to those with deep invasive tumours who have a 60% survival rate. Importantly, patients with tumours less than 5 mm from the serosal surface have a higher risk of recurrence and death than those with tumours more than 5 mm from the serosal surface^[17].

■ Lymph-vascular space invasion

Lymph-vascular space invasion (LVSI) seems to be an independent prognostic factor in terms of recurrence and survival from all histological types of endometrial cancer^[1, 15]. LVSI, however, correlates with depth of myometrial invasion, tumour grade and histological type. For example, the incidence of LVSI in early endometrial cancer is approximately 14% and it increases with tumour grade and depth of myometrial invasion. LVSI has been reported in 2% of grade 1 tumours, 5% of superficially invasive tumours, 42% of grade 3 tumours, and 70% of deeply invasive tumours^[15]. Others have reported an 83% five year survival rate for patients without demonstrable LVSI compared to a 64.5% survival rate for those with documented LVSI^[1].

■ Lymph node metastasis

Lymph node metastasis is the single most important prognostic factor in early-stage endometrial cancer. Morrow et al^[25] noted that the prevalence of pelvic lymph node metastases was 9.8% in stage I, and 36.5% in stage II disease.

In clinical stage I adenocarcinoma of the endometrium, a recurrence rate of 48% with positive lymph nodes has been reported, including 45% with positive pelvic nodes and 64% with positive aortic nodes, compared to 8% with negative nodes. The 5 year disease-free survival rate was 54% for patients with positive nodes compared to 90% for those without lymph node metastases^[21, 22]. Furthermore, the prognostic importance of aortic lymph node metastasis was emphasised in a study where 28 out of 48 (58%) patients with positive aortic nodes developed progressive or recurrent cancer, and only 36% of these patients were alive after 5 years, compared to a 11% recurrence rate and a 85% survival rate for patients without aortic node involvement^[25].

■ Tumour size

Tumour size is an independent significant prognostic factor for lymph node metastasis and survival in patients with endometrial carcinoma. The study of 142 women with clinical stage I endometrial cancer showed lymph node metastasis in 4% of patients with tumours ≤ 2 cm, in 15% with tumours > 2 cm, and in 35% of patients with tumours involving the entire uterine cavity^[30]. Analysing the same cohort of patients, a 98% five year survival rate for patients with tumours ≤ 2 cm, 84% for patients with tumours > 2 cm, and 64% for those with tumours involving the entire uterine cavity has been documented^[31].

■ Cervical extension

Involvement of the uterine isthmus, cervix or both is associated with a significant by increased risk of extra-uterine disease, lymph node metastasis, recurrence and poor survival. Patients with cervical involvement also tend to have higher grade, larger, and deep invasive tumours. Disaia et al^[10] reported that when the fundus of the uterus alone was involved, there was a 13% recurrence rate, in comparison with a 44% recurrence rate if the isthmus or cervix was involved. In surgically staged patients, the 5 year survival rate drops from 87% in stage I to 67.1% in stage IIb, when there is cervical stromal invasion (Adapted from the FIGO's Annual Report, vol. 23, 1998).

■ Intraperitoneal tumour

Extra-uterine metastases, excluding positive peritoneal cytology and lymph node metastasis, are of prognostic importance, influencing recurrence and survival rates. It has been shown that both the recurrence and 5 year disease-free survival rates were 50% for patients with extra-uterine disease, compared to a 11% recurrence rate and a 88% survival rate for those patients without intraperitoneal tumour^[21]. Parametrial metastases correlate with deep myometrial invasion, LVSI, and are responsible for a poor clinical outcome^[35].

■ Adnexal metastasis

In a review of 382 patients with endometrial carcinoma, 40 (10.5%) were found to have adnexal metastasis at surgical-pathological evaluation^[7]. In general, patients with adnexal involvement have other poor prognostic factors (particularly deep myometrial invasion, high-grade tumours, cervical involvement and lymph node metastases) that increase the probability of recurrence and distant metastasis. Recurrences in 14% of patients without metastasis to the adnexa have been reported, compared with a 38% recurrence rate in patients with adnexal metastasis. However, when adnexal spread is the only high-risk factor, the survival rate may be as high as 85%^[25]. In conclusion, it seems that adnexal metastases per se have little, if any, independent prognostic relevance.

■ Peritoneal cytology

The significance, prognostic implications and therapeutic management of patients with malignant peritoneal cytology in endometrial cancer remains obscure. Several authors have reported increased recurrence rates and decreased survival rates in patients with positive peritoneal cytology and have recommended treatment for these patients which has had no benefit.

The frequency of positive peritoneal cytology varies from 17% to 19% in stages I and II, and 68% to 85% in stages III and IV, respectively^[28]. Creasman et al^[8] reported positive peritoneal cytology in 26 (16%) out of 167 patients with clinical stage I endometrial carcinoma. Recurrences developed in 10 (38%) of these 26 patients, compared with 14 (10%) out of 141 patients with negative cytology. Morrow et al^[25] analysing 697 patients found that 25 (29%) developed recurrences when peritoneal cytology was positive for malignant cells, compared with 64 (10.5%) out of 611 patients with negative cytology. They observed that 17 of the 25 recurrences in the positive cytology group were located outside the peritoneal cavity. These and other studies have reported that positive peritoneal cytology is associated with poor prognostic factors. Lurain et al^[22] followed 157 clinical stage I endometrial cancer patients prospectively. Positive cytology was

neither significantly associated with nor an independent prognostic factor for recurrences. Importantly, it was also shown that patients with positive peritoneal cytology had several detrimental prognostic factors: 37% had deep myometrial invasion, 37% grade 3 tumours and 17% positive lymph nodes. It is therefore conceivable that positive peritoneal cytology, in the absence of these associated poor prognostic factors, has no impact on recurrence and survival.

■ Hormonal receptors

Sixty to 70% of endometrial carcinomas contain cytosolic progesterone receptors and/or cytosolic and nuclear oestrogen receptors. Both receptors are detectable in about 50% of endometrial cancer samples ^[18].

There is a close and direct relationship between receptor content and tumour grade, depth of myometrial invasion and lymph node metastasis. Furthermore, both oestrogen and progesterone receptor levels are independent predictors of survival for endometrial cancer patients. Women whose tumours are positive for one or both receptors have longer survival times than those whose tumours lack the corresponding receptors. The same study suggested that progesterone receptor levels seem to be a stronger predictor of survival, and the higher the receptor level the better the prognosis ^[9]. In addition, patients with receptor-positive metastatic tumours also have an improved survival rate ^[19].

■ Proliferation markers and genetic variables

It is clear that even surgical-pathological evaluation does not document the true biology of many endometrial tumours. Additional prognostic markers have therefore been studied. The analysis and prognostic significance of DNA ploidy, proliferative indices (S-phase fraction and Ki-67), and the genetic abnormalities in endometrial carcinoma involving several genes that encode for various cell cycle regulatory proteins, including K-ras, HER-2/neu, c-fms, c-myc, and P53, are the subject of subsequent chapters in this book. All these molecular markers hold potential prognostic implications that may alter the treatment strategy. It suffices to say that tumour aneuploidy has been correlated with high-grade tumours, deep myometrial invasion, advanced stage, and poor survival ^[2]. Some authors consider the S-phase fraction one of the best predictors of survival ^[26] while others find the expression of Ki-67 superior for this purpose ^[29]. Mutations of K-ras oncogene and P53 tumour suppressor gene, as well as over-expression/amplification of the HER-2/neu, c-fms, and c-myc oncogenes have been demonstrated in a significant proportion of endometrial carcinomas, and are associated with metastatic disease and diminished survival ^[13, 14, 24].

Recently, several other genetic perturbations with independent prognostic significance have been published. They comprise mutations of both tumour suppressor genes Rb2 and PTEN, and over-expression of bcl-2 protein and c-jun oncogene. Expression of cathepsin D and tumour angiogenic factors (e.g. PD-ECGF) and the analysis of tumour microvessel density have also been implicated as having prognostic importance in endometrial carcinoma.

As a concluding remark, it is hoped that in the near future this information will provide the development of new and improved therapeutic options for patients with high-risk cancer. Meanwhile, correlations have been demonstrated between the conventional prognostic variables, and both proliferation indices and molecular genetic abnormalities. These could assist identification, before surgery, of tumour subsets that are biologically more aggressive and that could benefit from newly devised therapeutic protocols.

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