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Endometrial Cancer: Forecast

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1. Introduction

Abnormal uterine peri- and postmenopausal bleeding represent more than two thirds of the Gynecological consultations and the primary exclusion target off such presentations would be endometrial cancer.(1)Endometrial cancer is the most common malignancy of the female genital tract in the world and the seventh most common cause of death from cancer in women in western Europe.(2)The disease thus motivates the development of adequate prognostic determinants for more accurate triage of patients through various treatment modalities and to provide better insight into the cell biology of the disease.In recent years, certain factors have led to an increasing awareness of and emphasis on diagnosis and treatment of endometrial cancer. These factors include the declining incidence of cervical cancer and related deaths in the United States, prolonged life expectancy, postmenopausal use of hormone replacement therapy, and earlier diagnosis. Moreover, the availability of easily applied diagnostic tools and a clearer understanding of premalignant lesions of the endometrium have led to an increase in the number of women diagnosed with endometrial cancer.(3)Screening for the disease and thus its prediction is highly recommended, however , there is overlap between the terms prediction and forecast, as prediction implies that some outcome is expected, while a forecast may cover a range of possible outcomes.(4)

2. Risk factors(5)

- Associated with increased risk:

Obesity, Menopausal estrogen use, Diabetes mellitus, Nulliparity, Hypertension, Late menopause, Early menarche (<12 yrs), Polycystic ovarian syndrome, and Gall bladder disease.

- *Associated with decreased risk*: Smoking & Oral contraceptives

3. Presentation

Most cases of endometrial cancer are diagnosed in early stages because of abnormal uterine bleeding as the presenting symptom in 90% of the cases. (6) It is still debatable, which diagnostic tool is best performing for patients with postmenopausal bleeding. Hysteroscopy and/or hysteroscopic guided endometrial biopsies as well as endometrial sampling tools almost exclusively replaced the older modalities for investigating such cancer such as dilatation and curettage (D&C).(7)

The Pap test helped somehow in the past through incidental detection of some early cases with endometrial cancer, however, the test was proven to be of too low sensitivity and positive predictive value in terms of detecting both cervical and endometrial cancers.[8]It must be remembered that screening refers to the evaluation of the asymptomatic patient. When bleeding occurs, evaluation becomes diagnostic rather than screening. A history of bleeding or demonstrated radiographic evidence of endometrial pathology removes a patient from the realm of screening and demands investigation, i.e., an endometrial biopsy.[9]

While screening for endometrial cancer has been evaluated in prospective studies, the efficacy of endometrial screening has never been evaluated in a large prospective randomized controlled trial.Endometrial biopsy is easily performed as an office procedure and has good sensitivity, with the small number of false negatives most likely a result of sampling error. Transvaginal ultrasound (TVU) has also been used as a noninvasive screening test to evaluate the endometrium.[9]

4. Diagnosis

4.1. Screening of asymptomatic cases for early detection

High index of suspicion must be maintained if endometrial carcinoma will be diagnosed at an early stage. Postmenopausal bleeding should be taken to mean endometrial carcinoma until proved otherwise.[10]

1. **Transvaginal sonography (TVS):** is used to assess the endometrial thickness. This has been used as screening method combined with outpatient suction endometrial sampling (e.g. using a pipette). The cutoff thickness (myometrium to myometrium) expected in postmenopausal women, was once thought to be up to 8 mm.[11] If the endometrium is thickened or insufficient material is obtained by biopsy for diagnosis, then a more invasive procedure is required. This ideally comprises hysteroscopy accompanied or followed by a diagnostic curettage.[11]However, as yet, there is no agreed-upon criterion for endometrial thickness that has both a high sensitivity and specificity; a high rate of false-positive results is also a limiting factor.[12]

Previous meta-analyses on endometrial thickness measurement probably have overestimated its diagnostic accuracy in the detection of endometrial carcinoma. We advise the use of cutoff level of 3 mm for exclusion of endometrial carcinoma in women with postmenopausal bleeding.[13]

TVS has the added advantage of detecting any ovarian lesion and assessing the extent of myometrial involvement of endometrial cancer which can be achieved as efficient as Magnetic resonance imaging (MRI) utilization for the same purpose.[14]

2. Progesterone challenge test (PCT):

It is a reliable, non-invasive test to determine if estrogens, either endogenous or exogenous, are present in sufficient quantity to cause endometrial proliferation. Postmenopausal women with intact uterus should be given 100 milligrams of progesterone intramuscularly, if withdrawal bleeding follows, this indicates high endogenous estrogen priming the endometrium denoting a high risk patient. On the other hand, negative PCT i.e. no withdrawal bleeding, indicates low endogenous estrogen and consequently low risk patient. The test should be repeated on annual basis for those patients. [15]

3. Endometrial sampling:

Cytological study: to detect exfoliated malignant endometrial cells by a cervicovaginal smear or jet lavage aspiration. It, unfortunately, gives less reliable results than expected with a sensitivity of not more than 50%. (16)

Endometrial tissue biopsy: Accepted as a first step in evaluating a high-risk patient for endometrial carcinoma, with a diagnostic accuracy of 90 – 98%.

The endometrial tissue biopsy can be obtained using:

- Vacuum aspiration: using Carman's cannula which is 3-4mm diameter suction curette with 300-600 mm Hg negative pressure.
- Intrauterine brushing: using a metallic wire with nylon bristles rotated all over the uterine cavity.
- Novak or Randall curette: office procedure, without anesthesia, where scrapes are taken from each uterine wall and sent for histopathological examination.(17)

4.2. Diagnosis of symptomatic cases with postmenopausal uterine bleeding

Diagnostic curettage has been the standard means for the diagnosis of endometrial pathology. The naked-eye picture can be suggestive of malignancy if the curettings are profuse, in the form of cheesy lumps rather than strips and if they are dark in color. Failure of the uterine wall to "grate" with curetting is suggestive. However, histopathological confirmation should be-awaited.(18)

Fractional curettage (samples taken from the endocervix then from the endometrial cavity) can also be used to diagnose or exclude cervical involvement and thus for clinical staging. (19)

Hysteroscopy can be used in the diagnosis of endometrial carcinoma. Because 15-20% of the uterine cavity with possible malignant growth could be missed in conventional curettage, hysetroscope allows inspecting the endometrial cavity and indicating the site from which endometrial biopsy is to be taken under vision.(20)

4.3. Genetic analysis

Genetic testing for mutations in the mismatch repair genes is available, and if a pathogenic change is found within a family, predictive testing becomes available for unaffected family members to assess microsatellite instability, a feature of mismatch repair genes mutation.(21) On the other hand, immunohistochemical staining for p53 gene demonstrating overexpression of p53.(22)

Final diagnosis for pretreatment assessment and staging must entail:

Radiological imaging:

- Computer axial tomography (CT) scan with contrast can be helpful in pretreatment staging by identifying the depth of myometrial invasion, abdominal lymph node involvement, spread to pelvic and extra-pelvic organs, and ureteric invasion. (23)
- Magnetic resonance imaging (MRI) is a more advanced diagnostic tool in pretreatment staging with more accuracy and can detect much smaller tumor deposits and early cervical involvement.(24)

- Intravenous urography (IVU) to check for ureteric involvement.
- Plain X-ray chest to detect lung secondaries in advanced stage of the disease.
- Radioisotope scan to detect distant metastasis and bone deposits.
- Lymphangiography: for lymph node involvement for preoperative staging; it is now, however, replaced by CT scan.[18]
- Endoscopy: (in advanced cases)
- Cystoscopy: to detect bladder infiltration.
- Sigmoidoscopy: to check for rectal and sigmoid colon infiltration.[18]

4.4. Biochemical markers related to endometrial carcinoma:

Gynecologists happen to experience that patients with tumors that are identical in grade and stage often have significantly different clinical outcomes or responses to therapy. In order to identify an objective biological factor correlating with tumor aggressiveness, many tumor markers have been investigated. So far, **CA125** is one of the most reliable tumor marker for adenocarcinoma of the uterus and frequently used in a clinical setting. Elevated CA-125 levels have also been observed in serum, menstrual effluent, and the peritoneal fluid of women with endometrial carcinoma.[25]It can be assumed that if a patient with endometrial cancer had an elevated preoperative CA 125, it would probably be a cancer with poor prognosis. Thus, CA 125 is considered a positive marker in these cases and its high production is associated with increased metastatic potential. In addition, CA 125 levels were found to be independent risk factor for pelvic lymph node metastasis.[26, 27]

Not only in the sera of patients with endometrial carcinoma, do CA 125 levels rise significantly, but also in their tissues. Cancer tissues contain CA 125 and the percentage of positive CA 125 tissue staining is significantly higher than that of elevated CA 125 serum levels. An increase in serum CA125 after operation predicted the possibility of recurrence. [28, 29]

The potent cytokine; tumor necrosis factor alpha **(TNF-α)** was first identified to be synthesized and secreted by the human endometrium. The endometrial epithelial cells are a major source of TNF-α. TNF-α may be useful in the discrimination of malignant from benign gynecological diseases and in monitoring tumor activity in patients early in the malignancy process. [30, 31, 32]

Tumor necrosis factor alpha (TNF α) concentration was determined by a solid phase immunoradiometric assay. The rate of abnormally high values of serum TNF α increased with advancing stage of the disease. On the other hand, serum TNF α level in cases of endometrial hyperplasia was significantly lower than in healthy individuals. It seems that the rise of serum TNF α in cases of endometrial carcinoma represents a possible mechanism of immune surveillance. It is thus suggested that serum TNF α estimations for the differential diagnosis of benign and malignant lesions of the endometrium in women with postmenopausal bleeding could be beneficial. [33]

4.5. Prognostic factors[19]

Multiple factors have been identified which significantly influence the prognosis in endometrial carcinoma; some of these factors are interdependent:

Prognostic factors in endometrial carcinoma:

1. Age and body morphology.
2. Stage.
3. Histopathologic type.
4. Histologic differentiation.
5. Depth of myometrial invasion.
6. Lymph node involvement.
7. Peritoneal cytology.
8. Steroid receptor status
9. DNA ploidy.
10. Molecular indices.

1. Age and body morphology:

Older patients do worse. Obese patients do better than lean ones. It seems that the obese, hyperlipidemic women, with evidence of unopposed estrogen exposure like anovulatory uterine bleeding, infertility, late menopause, and hyperplasia of ovarian stroma tend to have more differentiated endometrial carcinoma with better prognosis.

2. Stage:

Involvement of the cervix definitely worsens the prognosis; cervical stromal invasion is worse than involvement of the endocervix only. The overall survival rate for endometrial cancer is high as there is a preponderance of women diagnosed with stage I disease.

3. Histological type:

The rare tumor types of endometrial carcinoma like serous papillary, clear cell and squamous carcinoma have a definitely poorer prognosis than usual enometrioid adenocarcinoma. The frequent presence of squamous metaplasia not showing malignant feature i.e. adenoacanthoma, does not change the prognosis.

4. Histological differentiation: Tumor grade:

As the tumor gets less differentiated, the risk of deep myometrial invasion increases. Within each stage the prognosis is therefore, influenced by the tumor grade.

5. Depth of myometrial invasion:

Deep invasion is associated with higher rates of lymph node involvement and is usually associated with lesser degrees of differentiation. Reaching the serosa will shift the disease to stage III and is associated with poor prognosis.

6. Lymph node involvement:

There is a good deal of correlation between lymph node involvement and other prognostic factors. In stage I disease, the incidence of pelvic lymph node involvement is about 10 % and the 5-years survival in these subset is only 30% as compared with more than 70% for the whole of stage I cases. (34)

7. Peritoneal cytology:

Obtaining peritoneal washings for cytology examination is an easy procedure for assessment of prognosis. However, its value independent of other prognostic indicators is not fully established. (35)

8. Hormone (steroid) receptor status:

Estrogen receptor and progesterone receptor levels have been shown to be prognostic indicators for endometrial cancers independent of grade. Patients with tumors positive for one or both receptors have longer survival than patients whose carcinomas lack the corresponding receptors. Even patients with metastasis have an improved prognosis with receptor positive tumors. Progesterone receptor levels appear to be stronger predictors of survival than estrogen receptor levels, and the higher the absolute level of the receptor, the better the prognosis. (36)

9. DNA ploidy and proliferative index:

Flow cytometry has been used in assessment of the ploidy of the tumor. This determines cellular nuclear DNA content and measures the fraction of the tumor cells in proliferative phase (S- phase). Flow cytometry will determine DNA histogram, which reflects the cell cycle phase. G0 and G1 cells contain diploid nuclear DNA content. In a well-differentiated tumor, a smaller number of cells enter the S-phase and begin DNA replication (S-phase fraction). DNA ploidy can be denoted as DNA index (DI), which is the numerical ratio of DNA content of the tumor cells to the DNA content of G0/G1 peak of normal control population. A diploid tumor has a DI range of 0.95 % to 1.1 and a tetraploid tumor has a DI range of 1.9 to 2%; peaks outside these ranges e.g. 1.5 or 2.6 are defined as aneuploid. Most endometrial cancers are diploid but aneuploidy indicates advanced disease and a poor prognosis. A raised fraction of cells in the S-phase (with DI around 2) also indicates a poor prognosis.

10. Genetic and molecular markers:

Analysis of the mutations in mismatch repair (MMR) genes can be achieved through studying blood samples or tumor blocks to assess microsatellite instability, a feature of mismatch repair gene mutations. These mutations have been reported in 10% to 20% of endometrial adenocarcinomas. Alteration of the tumor suppressor gene p53 has also been demonstrated in about 20% of endometrial carcinomas and has been associated with papillary serous cell type, advanced stage and poor prognosis. (37,38)

In summary, endometrial cancer screening, and thus its outcome prediction (forecast) seem to be achievable in a more variety of ways than any other female genital malignancy. Early detection is definitely the first step to attain a complete cure. The management options for endometrial cancer, and thus the survival rate from the disease would depend largely on early detection modalities mentioned above. The following are some recommendations from the American cancer Society (ACS) for early detection of the disease based on patients' characteristics.(9)*Recommendations for Women at Average Risk:* There is no indication that screening for endometrial cancer is warranted for women who have no identified risk factors.(39)

Recommendations for Women at Increased Risk: There is no indication that screening for endometrial cancer should be recommended for women at increased risk for endometrial cancer because of history of unopposed estrogen therapy, late menopause, tamoxifen therapy, nulliparity, infertility or failure to ovulate, obesity, diabetes, or hypertension.[39]

Recommendations for Women at High Risk: The American Cancer Society recommends that annual screening for endometrial cancer with endometrial biopsy should be offered by age 35 for women with or at risk for hereditary nonpolyposis colorectal cancer (HNPCC). Women in this high-risk group should be informed about the risks and symptoms of endometrial cancer, and should be informed about potential benefits, risks, and limitations of testing for early endometrial cancer detection.

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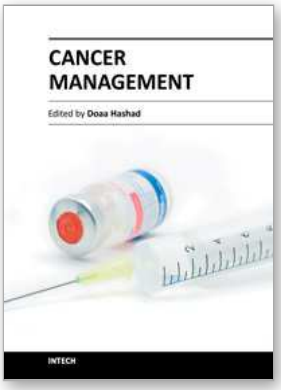

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