Prognostic and Predictive Factors in the Management of Carcinoma Endometrium

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Introduction

Carcinoma Endometrium is the most common gynecological malignancy in the west. It ranks third in India after cervix and ovary. Women with endometrial cancer are usually diagnosed at an early stage, as most present with irregular bleeding or abnormal vaginal discharge and surgery is curative. A few subset of women may present with high risk histological factors or are in an advanced stage of disease. These women will need multimodality treatment to achieve a cure. The overall 5-year survival is 80–90 % in stage 1 tumors. With the advent of molecular and genetic factors further research has to be progressed for the preoperative prediction of bad prognostic group to be selected for neoadjuvant treatment to improve the disease free survival.

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Prognostic and Predictive Factors

Various risk factors have been studied extensively since late 1970s [1, 2] which have a prognostic impact in the management of carcinoma endometrium. A prognostic factor is defined as a measurement taken at the time of diagnosis or surgery that is associated with outcome like overall survival, disease free survival, or local control. A predictive factor is a measurement that predicts response or lack of response to a specific treatment. Various risk factors include:

1. Stage of the disease
2. Type of the tumor
3. Grade of the tumor
4. Myometrial Invasion
5. Tumor site
6. Tumor size
7. Lymphovascular space invasion (LVSI)
8. Positive peritoneal cytology (PPC)
9. Adnexal metastasis
10. Peritoneal implants
11. Age

Stage of Disease

Surgicopathological staging is the most important prognostic factor directly correlating with the survival. However the role of clinicoradiological

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findings in staging is not insignificant. The new FIGO staging for carcinoma endometrium published in NCCN Version 1.2014 [3] is given in the Chap. 6 on Risk factors, diagnosis and staging.

In advanced stages, debulking surgery with radiotherapy with or without chemotherapy is usually done. Five-year survival in carcinoma endometrium is given below and the figures given below are from the National Cancer Database, and are based on women diagnosed with endometrial cancer between 2000 and 2002.

Stage	5 years survival (%)
1A	88
1B	75
11	69
111A	58
111B	50
111C	47
1v A	17
1v B	15

Types of the Tumor

There are two types of tumors.

Type I tumors usually occur in pre- and perimenopausal women, often with a history of unopposed estrogen exposure and/or endometrial hyperplasia. They are often minimally invasive into the underlying uterine wall and are of low grade endometroid type and carry a good prognosis.

Type II tumors occurs in older, postmenopausal, thin women, and are not associated with increased exposure to estrogen; they are more aggressive and less differentiated and carry a poor prognosis. These include clear cell tumor, papillary serous tumors, and carcinosarcomas. These tumors have mainly p53 mutation and ERBb-2 (her 2 neu) expression.

Myometrial Invasion

Depth of myometrial invasion, tumor extension to the cervix, and lymph nodal status are part of FIGO staging, each of the above factor involvement progressively upstages the disease and they are independent prognostic factors themselves. Increasing depth of myometrial infiltration is associated with increasing tendency to extrauterine spread. Superficial or no myometrial infiltration is seen with well differentiated tumors. Deep myometrial invasion is seen frequently in poorly differentiated and undifferentiated tumors and thus is an alarming sign for lymph nodal involvement and distant metastasis and is often independent of degree of differentiation [4, 5]. Patients with >50 % involvement of myometrium is associated with poor prognosis. Patients whose myometrium has not been involved do not have much lymph-vascular space invasion even [6].

Deep myometrial involvement often coexists with cervical involvement by endometrial adenocarcinomas and has an adverse effect on prognosis [7]. Patients with lower uterine segment involvement are more likely to have pelvic and paraaortic nodal disease, and increasing local recurrence [8]. Spread to lymph nodes is associated with poor prognosis and require adjuvant treatment.

Tumor Size

In majority of tumors, T stage includes tumor size, the larger the tumor the more advanced the stage and lesser the survival. In endometrial carcinoma, increasing T stage indicates increasing depth of uterine wall infiltration. However many authors could correlate increasing tumor size with poor outcome in uterine carcinomas [8]. The conventional threshold is a measure of 2 cm [9]. Some have attempted to quantify three-dimensional tumor volume and correlate this risk to metastatic spread and survival [10].

Tumor Site

Tumor location inside the uterus can predict distant nodal disease and indicate chance of recurrence. Tumor involving fundal region has

increased risk of paraaortic lymph node involvement. Tumor occupying the whole endometrial cavity significantly upstages the cancer [11] (Fig. 12.1, and Table 12.1).

Grade of the Tumor

Since long, grade of the tumor has been regarded as an important prognostic factor in endometrial cancer [12]. Adenocarcinomas having 5 % or less nonsquamous or nonmural solid growth are designated as grade 1, those with 6–50 % solid growth as grade 2, and those with more than 50 % solid growth as grade 3. The 5-year survival rate in stage 1 carcinoma endometrium depends on the grade; the higher the grade, the poorer the prognosis (Tables 12.2 and 12.3)

Peritoneal Cytology

Positive peritoneal cytology portends a poor prognostic factor in earlier studies [1, 13]. The impact on survival of positive peritoneal cytology in the absence of other extrauterine disease is unclear and the treatment aimed at this is not well founded [14]. The following mechanisms may be deduced from the literature *for the presence of malignant cells in the peritoneal cavity* [15, 16]. (1) Result of transtubal transport; (2) direct

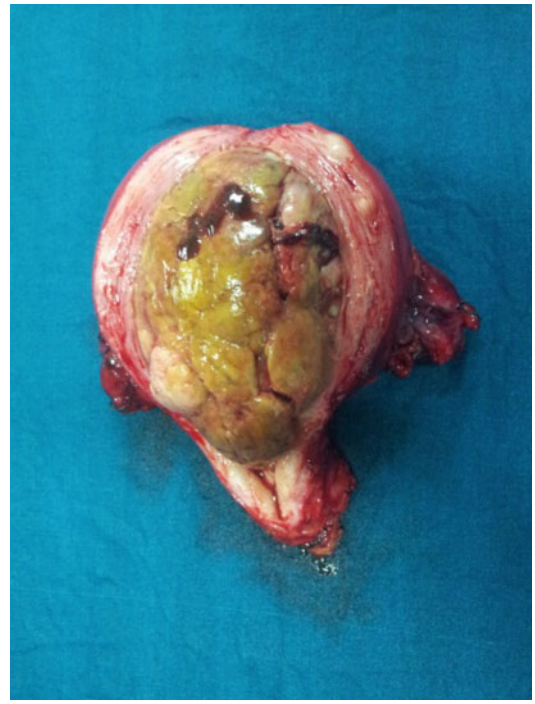

Fig. 12.1 Tumor occupying whole of the endometrial cavity

Table 12.1 Shows the tumor location inside uterus affecting the spread [11]

Tumor Site	Nodal spread (%)	Cervical Stromal Involvement (%)	Regional spread (%)	Metastasis (%)
Anterior (n=5)	0	0	0	0
Posterior (n=7)	0	14.28	0	0
Ant+post (n=3)	0	0	0	0
Fundal (n=5)	20	0	0	0
Ant.Fundal (n=5)	20	0	0	20
Post.Fundal (n=5)	0	0	0	0
Ant.+body (n=1)	0	0	0	0
Full Endometrial.Cavity (n=21)	28.57	14.28	19.04	4.76
Missing (n=7)	0	0	0	0

Table 12.2 Five-year survival in stage 1 endometrial cancer

Grade	Surgical (%)	Clinical (%)
1	93	60
2	90	50
3	79	29

Survival rates based on 5219 patients (Pecorelli S: Int J Gynecol Obstet. 2006;95:S121)

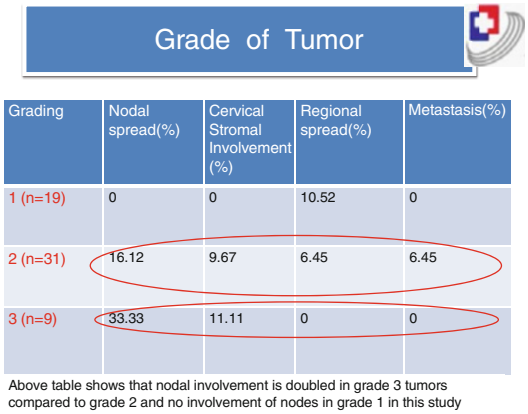

Table 12.3 Grade of tumor and spread [11]

extension of tumor through the myometrium; (3) lymphatic metastasis to the peritoneal cavity; and (4) reflection of multifocal peritoneal occult spread. Transtubal transport seems to be the most logical and popular. In more recent studies the authors are of opinion that the presence of positive peritoneal cytology is not an independent prognostic factor, and that it does not seem to reflect the potential of peritoneal spread in patients with endometrial carcinoma confined to the uterus [17, 18]. **Positive peritoneal cytology** is removed from FIGO Staging now; however it should be documented separately.

Patients having **adnexal metastasis and peritoneal implants** have poor prognosis as they indicate extrauterine spread and have more chances of pelvic and paraaortic lymph nodal involvement.

Age

Endometrial cancer occurs rarely in women under the age of 40. Most cases are found in women aged 50 and over, with more than half of the cases diagnosed in the age group of 50–69. The risk of endometrial cancer increases as the woman gets older. Age is not a significant variable of outcome after adjusting for other poor prognostic factors [19]. One study [20] divided patients to two groups, age in Group A was 59 years (range 50–69) and Group B was 75 years (range 70–92). Patients in Group B were more likely to have hypertension and coronary artery disease. There were no differences in progression-free or disease-specific survival; however, Group B had a worse overall survival proved to be due to associated comorbidities.

Many studies addressed the value of race as a prognostic factor in carcinoma endometrium [21–23]. Analysis of 41,120 cases of endometrial cancer indicated that race was a prognostic factors in addition to FIGO stage, histology, histologic grade, lymph node status, and age at diagnosis [21]. When incorporating the number of poor prognostic factors in a survival model with race and surgical stage, race ceased to be of significant prognostic value [22]. Although the incidence of endometrial cancer is less in Black women, cancer specific survival rates were lower in them when compared to that in white women. This racial difference in survival is multifactorial and include later diagnosis, treatment disparities, comorbid conditions, and genetic differences which result in the occurrence of more aggressive tumors in Black Americans [23].

DNA Ploidy

In a recent study [24], predictive and prognostic factors were analyzed in a consecutive series of 4543 endometrial carcinomas and it was concluded that DNA ploidy was an independent and significant prognostic and predictive factor. Eight predictive and prognostic factors were analyzed in this study with regard to recurrence and survival. The factors analyzed were: age, FIGO stage, histology, FIGO grade, nuclear grade, DNA ploidy, myometrial infiltration, and p53 expression. The 5 years actuarial locore-

gional recurrence rate was 3.6 %, the factors which independently affected the recurrence rate were FIGO grade, DNA ploidy, and depth of myometrial infiltration. The 5 years actuarial overall survival rate in these patients was 73 % and cancer specific survival was 83 %. All the factors studied except p53 expression analyzed with immunohistochemistry were found to be significantly affecting overall and cancer specific survival rates. Tumor stage was the single most important factor with a risk ratio of 4.2 followed by FIGO grade 2.5 and 1.6 for DNA ploidy. Myometrial invasion had the lowest risk ratio of 1.3 in this study with regard to survival.

LVSI

Lymphovascular space invasion is an important predictor for prognosis of disease as these are the patients who are at high risk for recurrences. The risk of pelvic and paraaortic lymph node involvement increases significantly. Gadducci et al. [25] in 2009 reported that their univariate and multivariate analysis on 259 endometroid endometrial cancer patients showed lymphvascular space involvement (LVSI) and deep myometrial invasion as the independent predictive variables for the risk of distant hematogeneous failure. The analysis included 12 patients in stage 1B-2 who developed distant failure compared to 20 randomly chosen control group who were disease free after a median period of 52 months.

In multivariate analysis of 324 high intermediate and high risk endometrial cancer patients (stage 1–3), who came for adjuvant radiotherapy in Maccallum Cancer Centre, for relapse, positive LVSI had a hazard ratio of 4.9, which increased to 8.8 in the presence of positive nodes [26]. For overall survival, only LVSI was significant, with a hazard ratio of 3.02. In particular, in the presence of LVSI and nodes, histological type, grade, and myometrial invasion were not significant factors. Five hundred twenty-five endometrial cancer patients who underwent primary surgery were assessed for the impact of LVSI on recurrence and survival [27].

LVSI in this study was associated with a high risk of recurrence and poor overall survival in early stage endometrial cancer; therefore, it is prudent to include evaluation of lymph vascular space involvement in the clinical decision to decide whether or not a patient with early stage endometrial cancer should receive adjuvant therapy.

Risk group definition [24] is very important in predicting prognosis: apart from pathological factors DNA ploidy is also included in this risk categorization.

The definition of high-risk carcinomas was as follows: (1) FIGO stage I, (2) nonendometrioid histological type, (3) presence of two of the following risk factors: FIGO grade 3 (poorly differentiated), deep (≥50 %) myometrial infiltration, DNA aneuploidy (FCM), (4) nuclear grade 3, (5) pathologically negative lymph nodes, and (6) negative abdominal cytology. Points 5–6 were optional in this study, and data are not available for all cases.

The definition of medium-risk carcinomas was as follows: (1) FIGO stage I, (2) endometrioid histological type, (3) presence of one of the following risk factors: FIGO grade 3 (poorly differentiated), deep (≥50 %) myometrial infiltration, DNA aneuploidy (Flow cytometry (FCM)), (4) nuclear grade 1–2, (5) pathologically negative lymph nodes, and (6) negative abdominal cytology. Points 5–6 were optional in this study, and data are not available for all cases. Lymph vascular space invasion (LVSI) was not regularly included in the pathology reports at the participating centers and was not included in the definition of the medium-risk group.

The definition of low-risk carcinomas was as follows: (1) FIGO stage I, (2) endometrioid histological type, (3) presence of none of the following risk factors: FIGO grade 3 (poorly differentiated), deep (≥50 %) myometrial infiltration, DNA aneuploidy (FCM), or (4) nuclear grade 3. All pathology reports were reviewed by one experienced pathologist at the regional referral center.

It is interesting to note that 54 % of all endometrial tumors will come under the low risk category and 22 % will come under high risk category. The low risk and high risk groups significantly differ in their survival outcomes, with the high risk group getting only 50 % cancer specific survival. The risk grouping helps oncologist to discriminate between patients who require surgery alone (low risk), who require surgery plus brachytherapy (intermediate risk), and those who require external beam radiation and chemotherapy in addition to surgery [28–30].

Tumor Markers as Prognostic Factors in Endometrial Carcinoma

CA 125 as a prognostic factor was studied by Espino-strebel and Luna [31] in 90 patients. They concluded that Ca 125 was significantly correlated with deep myometrial invasion, adnexal metastasis, pelvic and paraaortic nodal involvement, and recommended routine preoperative Ca 125 estimation. A receiver operating characteristic curve (ROC) was constructed to determine Ca 125 cutoff value. A cutoff value of 55 U/ml can predict extrauterine spread with sensitivity of 53.85 %, specificity of 84.38 %, and accuracy of 75.56 %.

Denschlag et al. [32] analyzed 101 patients of stage 3 endometrial cancer to find the prognostic factors of treatment outcome. They observed that an elevated Ca 125 level, adnexal involvement, the final tumor grade, and the lymph node dissection were independent predictors of cause-specific survival.

In multivariate analysis of the results of 100 normal subjects, 47 patients with benign gynecological diseases and 97 patients with endometrial cancer [33] found CA15.3 to be highly significant and had a larger hazard ratio. Univariate analyses showed that the increase of all the three, CA125, CA15.3, and CA19.9, were significantly associated with shorter survival.

Biological and Molecular Prognostic Factors

Among the oncogene expressions, the widely studied one is Her-2neu oncogene expression. Hetzel et al. [34] found Her-2neu oncogene's overexpression to be associated with a poor overall survival. The fraction of cells in S-phase has also been found to be an important prognostic indicator of clinical outcome [35].

Salvesen et al. [36] reported a population based study in 1999 and concluded that in addition to age and FIGO stage, microvessel density and Ki67 and P 53 protein expression were independent prognostic factors in endometrial carcinoma.

A number of authors [37–39] emphasize the prognostic importance of progesterone receptors. Ingram et al. [40] found it to be the most significant prognostic factor in stage 1 and 2 patients. In their series, the 3-year survival tripled (93 %) in patients with progesterone receptor level more than 100 compared to patient with levels less than 100 (36 %).

Lack of PR expression is a strong, independent risk factor for tumor recurrence in patients with stages I–II endometrioid endometrial cancer. The use of this easily measurable biomarker as a prognostic factor in the clinical context should be considered [41]. Molecular markers were detected by the immunohistochemistry on 200 endometrial cancer patients and Yao et al. [42] found the expression rates of ER, PR, PTEN, and p53 were 86.5 %, 85.5 %, 82.1 %, and 49.2 %, respectively. The expression level of Ki-67 in the tumor tissues was 46.9 % ± 24.7 %. The PR expression had a negative correlation with FIGO staging, histological grade, and depth of myometrial infiltration. They concluded that the value of estimating the prognosis using the expressions of ER, PTEN, p53, and Ki-67 was negative, except for the expression of PR.

Alteration of pRb expression is uncommon in endometrial carcinoma and when it does occur, it may represent a late event in carcinogenesis. Loss of heterozygosis (LOH) at the Rb locus

occurs in 10–18 % of endometrial carcinomas; however, there is no significant correlation between Rb LOH and clinicopathological factors.

The role of pRb2/p130 in endometrial carcinogenesis appears more relevant. Reduced expression of pRb2/p130 is a strong independent predictor of poor outcome in endometrial cancer [43]. Increased levels of expression were significantly associated with increased disease free survival. In a multivariate analysis, pRb2/p130 status, tumor stage, and ploidy status were independent predictors of clinical outcome and the risk of dying of disease was increased substantially among patients with loss of pRb2/p130 in tumor cells.

High expression of pRb2/p130 is seen in proliferative endometrium and in hyperplasia without atypia and downregulation in secretory endometrium, atypical hyperplasia and carcinoma [44] suggesting that Rb2 expression might be estrogen-regulated.

In type I endometrial cancer, PARP1(+), ATM(+), and FANCD2(+) were associated with high tumor grade, and γH2AX(+) and ATM(+) with tumor recurrence. In type II endometrial cancer, only PARP1(+) was associated with tumor stage. Endometrial carcinoma patients with p53(+) or FANCD2(+) were more likely to recur with 5-year recurrence free survival (RFS) probability of 71.4 % in comparison to 85.5 % for the other patients and they were more likely to have shorter 5-year overall survival [45].

Phosphatase and tension homology deleted on chromosome ten (PTEN), a new candidate tumor suppressor gene, was the first gene that was found to be phospholipase tumor suppressor gene. Loss of PTEN expression is an early event in endometrial tumorigenesis [46]. Loss of PTEN expression in patients with endometrial carcinoma was significantly related to histological classification and differentiation. PTEN loss was found in 56.8 % of tumors, and occurred more often in EC (60.7 %, 51/84) than in NEC (27.3 %). Loss of PTEN staining was significantly related to the advanced staging in the grade 1 (G1) and grade 2 (G2) endometrioid adenocarcinoma group. PTEN may interfere with the process of apoptosis and cell proliferation by promoting survivin expression [47]. Survivin is a member of the inhibitor of apoptosis proteins, which also has a role in the control of cell division.

High P53 expression correlates with morphological features of aggressiveness. Positive staining was associated with increased surgicopathological staging , histological grade, and lymph node metastasis [48]. p53 staining was largely found in grade 3 (G3) endometrioid adenocarcinoma and other phenotypes of endometrial cancer. Simultaneous abnormality of p53 and PTEN often occurred at a late phase of carcinogenesis [49]. Phosphorylated protein kinase B(p-AKT) was positive in 53.7 % (51/95) of tumors and was found to express almost similarly in endometrioid adenocarcinoma(EC) and nonenometrioid adenocarcinoma (NEC). There was no significant difference of patient survival between p-AKT positive and negative subgroups. p-AKT positive and PTEN loss might have synergic effect on tumor proliferation. On the other hand, as p-AKT expression did not have any correlations with PTEN, P53, and HER-2 status [50]. Ugaki et al. [51] also reported that the patients with PTEN-positive and p-Akt-negative expression clearly showed a higher survival rate than patients in the other groups.

BAF 25 (ARIDIA) is a driver gene; its loss is a frequent event in high grade endometrial carcinoma. The prognostic significance of ARIDIA loss is controversial. ARIDIA loss occurs secondary to deregulated mismatch repair (MMR) mechanism. BAF 25 loss is seen in 29 % of high grade endometrial carcinoma which included high grade endometrial carcinoma, serous carcinoma, and clear cell and carcinosarcomas. Loss of MMR is observed in 33 % of cancers. BAF 25 loss goes hand in hand with MMR deregulation mechanisms. Since MMR deregulation mechanisms represents an alternative oncogenic pathway to P53 alteration, ARIDIA loss is found to be associated with normal P53 expression. BAF 25 loss is associated with superior survival in clear cell and carcinosarcoma [52] (Table 12.4).

Table 12.4 Biological and molecular factors and their effect on outcome of endometrial cancer

	Favorable	Unfavorable
Progesterone receptor	High expression	Reduced expression
pRB	High expression	Reduced expression
PTEN	High expression	Loss
p53 staining	Negative	Positive
Her-2/neu	Reduced expression	Overexpression
pAKT	Negative	Positive
Aridia	Loss	Expression
PARP	Negative	Positive
ATM	Negative	Positive
FANCO2	Negative	Positive

Summary

The classification of Endometrial Carcinoma into Type I and Type II provides a basic criterion to decide the extent of surgical staging procedures and treatment protocols. In FIGO stage I itself, apart from histology which is the basis of Type I and Type II classification many predictive and prognostic factors are incorporated to categorize it into three risk groups for predicting the outcome. CA 125 if elevated indicates extrauterine disease. Progesterone receptor expression in addition to predicting prognosis indicates favorable response to progesterone treatment and is a part of uterine preservation protocol. Many other molecular prognostic factors like PTEN, P53, and Her2neu also provides an insight into the survival outcomes.

Key Points

1. Depth of myometrial invasion, tumor extension to the cervix, and lymph nodal status are part of FIGO staging each of whose involvement progressively upstages the disease and each of which are independent prognostic factors themselves.
2. Grade of tumor and DNA ploidy are significant risk factors which decides intensity of spread and survival.
3. Tumor occupying the whole endometrial cavity significantly upstages the cancer.
4. It is prudent to include evaluation of lymph vascular space involvement in the clinical decision adjuvant therapy in early stage disease since these are the patients at risk of recurrence.
5. The risk grouping helps oncologist to discriminate between patients who require surgery only (low risk), or combined treatment.
6. An elevated Ca 125 was significantly correlated with deep myometrial invasion, adnexal metastasis , and pelvic and paraaortic nodal involvement.
7. Loss of PTEN expression rate is more in endometrioid adenocarcinoma and is associated with advanced stage and poor prognosis.
8. Positive p53 staining is associated with biological aggressiveness.
9. Aridia (BAF 25) loss is a frequent event in high grade endometrial carcinoma. Aridia loss is associated with superior survival in clear cell and carcinosarcoma.

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