Yonsei Medical Journal
Vol. 43, No. 6, pp. 769 - 778, 2002

Clinicopathologic and Biological Parameters Predicting the Prognosis in Endometrial Cancer

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Endometrial carcinoma is the most common malignancy of the female genital tract in United States or Europe, but in Korea, its incidence is comparatively low than that of cervical cancer of uterine cervix. Recently the prolonged life expectancy, postmenopausal use of hormone replacement therapy, and the availability of easily applied diagnostic techniques have led to increasing incidence of endometrial cancer. Although during the past several decades, the histopathology, spread patterns, and prognostic factors of endometrial cancers have been better defined, the clinicopathologic and biologic prognostic parameters should be further evaluated for the better treatment results in endometrial cancer.

Key Words: Endometrial cancer, clinicopathologic parameters, biological parameters

INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy affecting women in United States or Europe, but in Korea, its incidence is comparatively low than that of cervical cancer of uterine cervix. According to the statistics reported by the Cancer Committee of Korean Obstetrics and Gynecology Association,[1] 406 endometrial cancer, 862 ovarian cancer, and 3117 cervix cancer was newly diagnosed in 1998, and as expected, cervix cancer was the most common malignancy in female genital tract. But the prolonged life expectancy, postmenopausal use of hormone replacement therapy, and the availability of easily applied diagnostic techniques have led to increasing incidence of endometrial cancer.[2] The incidence of endometrial cancer in our institute showed an increase from 1970's, and during the first 2 years of the 2000's, 68 cases have been reported which is an abrupt increase comparing to the past experience.

Although endometrial cancer usually presents as stage I disease and can generally managed with good prognosis,[3,4] in advancing stage, it shows a poor prognosis as in other malignancy of the female genital tract.

During the last 20 years many studies underwent to evaluate the prognostic parameters of endometrial cancer, because the prognostic factors are important in deciding further treatment modalities such as chemotherapy or radiation. The application of the 1988 FIGO surgical staging system provided histopathologic information that was essential for the prediction of the prognosis. The information acquired through surgical staging are much accurate compared to those acquired by imaging studies. Adding to that, the recent progress in molecular biology introduced new concepts in biological prognostic parameters, which are oncogene and tumor suppressor gene. The clinico-pathologic and biologic prognostic parameters should be further evaluated for the better treatment results in endometrial cancer.

Received September 4, 2002

This study was supported by Brain Korea 21 Project for Medical Science, Yonsei University.

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PROGNOSTIC PARAMETERS

Clinicopathologic prognostic parameters

Total hysterectomy and bilateral salpingo-

oophorectomy are the primary operative procedures for stage I and II endometrial cancer. Radiotherapy is used postoperatively for the prevention of recurrence, but its timing and indication have not reached consensus. Variable opinions exist in deciding the extent of surgical treatment, and Disaia & Creasman reviewed the prognostic factors, surgery, and radiotherapy before and after surgery in retrograde analysis.[3] For the replacement of clinical staging, the FIGO published a surgical staging system in 1988. Using the FIGO surgical staging system, prognosis of the patient could be predicted, and postoperative treatment such as radiotherapy, chemotherapy, or hormone therapy could be planed accordingly.[5-7] Prognostic parameters other than myometrial invasion, lymph node metastasis, or histologic grade are under investigation by many researchers; the clinicopathologic prognostic parameters are listed in the Table 1.

Table 1. Clinicopathologic Prognostic Factors in Endometrial Cancer

1. Age
2. Stage
Histologic grade
Myometrial invasion
Peritoneal cytology
Adnexal involvement
Isthmus-cervix extension
Lymph node metastasis
3. Histologic type
4. Lympho-vascular space invasion
5. Tumor size

Age

In general, younger women with endometrial cancer have a better prognosis than older women.[8] Poor prognosis in older patients has been related to a higher incidence of grade 3 tumors or unfavorable histologic subtypes. Aalder et al. reported a 6.1% mortality and recurrence rate in patients under 60 years of age, but the rate increased to 12.3% in patients older than 60 years of age.[9] But stratifying the histologic grade, the age factor did not work as an independent prognostic parameter, and no consensus has been reached in confirming its significance.[8,10]

Stage

The stage of disease is the most significant variable affecting survival. Before the publication of the 1988 FIGO system, Kottmeier et al. reported 5-year survival rate based on the 1971 FIGO clinical staging system; the 5-year survival rate in stage I endometrial cancer was 74.2%, in stage II 57.4%, in stage III 29.2%, and in stage IV 9.6%.[11] Lymph node metastasis was demonstrated in 8.2% of stage I, but 43.8% in stage IV; lymph node metastasis was more frequent in advanced stages. Abeler et al. reported the 5-year survival rate based on the 1988 FIGO surgical staging system; comparing the result to that of the clinical staging system, the 5-year survival rate was lower in the patients staged surgically, except in stage I.[12] In our institute, we analyzed 99 endometrial cancer patients; 66.7% (66 cases) were stage I, 16.1% (16 cases) stage II, 12.2% (11cases) stage III, and 6.0% (6 cases) stage IV. The recurrence rate in our study was 5.3% (2 cases) in stage I, 20% (2 cases) in stage II, 40% (4 cases) in stage III, and 55.5% (5 cases) in stage IV.

In surgical staging, factors such as lymph node metastasis, histologic grade, myometrial invasion, peritoneal cytology, adnexal involvement, and isthmus-cervix extension is considered. Therefore, staging can be considered as the most significant prognostic parameter.

Prognostic variables associated with stage

Histologic grade

Histologic grade is strongly associated with prognosis, lymph node metastasis, and myometrial invasion. Creasman et al. reported more than 2/3 myometrial invasion in 42% of grade III patients,[13] whereas Boronow et al. reported deep myometrial invasion in 4.3% of stage I grade I and 39% of stage I grade III patients; which signifies the association of histologic grade and myometrial invasion.[14] The 5-year survival rate was 81% in stage I grade 1 patients, but 50% in stage I grade 3 patients which showed statistical significance. The recurrence rate was 4% in grade 1 patients compared to 42% in grade 3 patients. In our study, 64 histologic grade defined cases, 33 cases were grade 1 and only 2 cases (6.0%) accompanied pelvic lymph node metastasis, but comparatively, in 19.0% (4 cases out of 21 cases) of grade 2 cases

showed pelvic lymph node metastasis. Only 10% of grade 1 (1 case out of 10 cases) showed pelvic lymph node metastasis, but 30% of grade 3 (3 cases) showed pelvic lymph node metastasis, which supports the association between high histologic grade and lymph node metastasis, but it was not statistically significant.

Myometrial invasion

Myometrial invasion along with histologic grade functions as important prognostic parameters. Deep myometrial invasion is associated with poor survival rate. Boronow et al. reported 8% recurrence rate in patients with endometrial cancer limited to endometrium, but the risk of recurrence increased in patients with deep myometrial invasion.[14] Jones et al. reported the 5-year survival rate to be 80% in patients without myometrial invasion, but it decreased to 60% in patient with deep myometrial invasion.[15]

Peritoneal cytology

Reports on peritoneal cytology as a prognostic parameter are still controversial; Creasman et al. reported 16% of clinical stage I to be peritoneal cytology positive.[16] Positive peritoneal cytology may be influenced by histologic grade, adnexal involvement, myometrial invasion, and lymph node metastasis, therefore it cannot be considered as an independent prognostic factor. There have been postulations about positive peritoneal cytology to have association with other prognostic parameters but the comparison of peritoneal cytology positive and negative groups didn't show statistical significance. Especially, in cases of positive peritoneal cytology without other prognostic parameters positivity, it cannot predict the recurrence or survival rate. In contrast, if the positive peritoneal cytology is associated with adnexal involvement and lymph node metastasis, it can influence the survival and recurrence rate.[17,18]

Adnexal involvement

About 7% of stage I endometrial cancer is inadvertently found after surgery of endometriosis. In cases of myometrial or isthmus-cervix extension, there is a higher probability of lymph node metastasis and adnexal involvement. Positive peritoneal cytology is demonstrated in 60% of cases with adnexal spread; 38% recurred in cases with adnexal spread, whereas only 11% recurred without adnexal spread.[16]

Isthmus-cervix extension

Endometrial cancer extending to isthmus and cervix is considered to be clinical stage II, which is usually associated with myometrial involvement, higher rate of lymph node metastasis (23-35%), and poor prognosis. Occasionally, endometrial cancers which were not detected in endometrial biopsy or endocervical curettage, are detected after total hysterectomy; changes in stage after surgical staging is possible, and accordingly prognosis may differ.[19] DiSaia et al. reported a higher survival rate in endometrial cancer with only endocervical glandular involvement, whereas that of the cervical stromal invasion was comparatively low.[20]

Lymph node metastasis

Lymph node metastasis varies with the clinical stage, length of uterine cavity, histologic grade, and myometrial invasion. The rate of lymph node metastasis increases in patients with advanced clinical stage, poor histologic grade, long uterine cavity length, and deep myometrial invasion. Creasman et al. reported a 57% recurrence rate and 32% mortality rate with lymph node metastasis, compared with 11% and 8% without it.[13]

Histologic type

The significance of histologic type in endometrial cancer has not reached the conclusion, but clear cell carcinoma and papillary serous carcinoma are said to have relatively poor prognosis. Abeler et al. reported a 42.3% 5-year survival rate in clear cell carcinoma compared with 27% in papillary serous carcinoma.[12] In our study, of the 101 cases of proven histologic type, 85 cases were adenocarcinoma, 9 were papillary serous carcinoma, 4 were adenosquamous carcinoma, and 3 were adenoacanthoma; comparing the 5-year survival rate, papillary serous carcinoma showed the worst rate where all 5 patients died.

Lymph-vascular space invasion (LVSI)

LVSI is observed in 15% of early stage endometrial cancer, and it is said to be an independent prognostic factor, although it increases with poor histologic grade and deep myometrial invasion.[12] Hanson et al. reported a 2% recurrence rate and

1% mortality rate for patients without LVSI, but the rate increased to 44% and 31% respectively for patients with LVSI.[21] Using multivariate analysis, controlling the histologic grade and depth of myometrial invasion, patients with LVSI showed a significantly higher recurrence rate.

Tumor Size

Tumor size is a significant prognostic factor for lymph node metastasis and survival in endometrial cancer. The rate of lymph node metastasis in stage I endometrial cancer was 4% in patients with tumor < 2 cm, 15% in patients with tumors ≤ 2 cm, and 35% in patients with tumor involving the entire uterine cavity. Five-year survival rates were 98% for patients with tumor ≤ 2 cm, 84% for patients with tumors ≥ 2 cm, and 64% for patients with tumors involving the whole uterine cavity.[22]

Biologic prognostic parameters

Ovarian hormones especially estrogen is said to play an important role in pathogenesis of endometrial cancer. The causal relationship between estrogen and endometrial cancer is postulated, because postmenopausal use of estrogen replacement therapy without progestins increased the risk of endometrial cancer. As the pathogenesis of colorectal cancer, endometrial hyperplasia representing a spectrum of morphologic and biologic alterations of endometrial glands and stroma, is said to progress to carcinoma with architectural abnormality and cellular atypia. But the molecular changes during the progression have not been studied conclusively.

The progress in molecular biology substantiated more than 60 proto-oncogenes, and the translocation, deletion, gene amplification, and sequence alteration is said to activate proto-oncogenes, which is ultimately involved in tumorigenesis. The alterations of oncogenes and tumor suppressor genes was demonstrated to play an important role in the pathogenesis of endometrial cancer, and the association between the gene abnormality, advanced stage, poor histologic grade, and poor prognosis has been established. Steroid hormone receptors, DNA flow-cytometric analysis and karyotyping, oncogenes, tumor suppressor genes, tumor markers, apoptosis related proteins, cell cycle related antigens, and factors associated with stromal invasion and metastasis are the proposed biological prognostic parameters in endometrial cancer (Table 2).

Table 2. Biologic Prognostic Factors in Endometrial Cancer

1. Steroid hormone receptors
2. DNA flow-cytometric analyses and karyotyping
3. Tumor markers
4. Oncogene and tumor suppressor gene
   1) Ras oncogene
   2) c-erb-2 oncogene
   3) c-myc oncogene
   4) p53 tumor suppressor gene
5. Apoptosis related proteins
   1) Bcl-2
   2) BAX
6. Cell cycle related antigens
   1) Ki67
   2) Cyclins
   3) CDK inhibitors
   4) AgNORs
   5) DNA polymerase α
   6) PCNA
7. Molecules associated with stromal invasion and metastasis

Steroid hormone receptors

Estrogen receptor (ER) and progesterone receptor (PR) levels have been shown to be prognostic indicators for endometrial cancer, having a reciprocal relationship with histologic grade.[23-27] Ito and Tagara(1993) reported a 90% ER positivity and 83% PR positivity in grade 1 cancers, compared to a relatively low 55% and 22% positivity in grade 3 cancers. In our study, due to small study population, the relationship between hormone receptor positivity and histologic grade could not be confirmed. Liao et al. reported PR as a stronger predictor of survival than ER, and even patients with metastasis had a better prognosis in receptor-positive tumors.[25] Morrow and Schlaerth reported a 90.9% response rate to progesterone treatment in ER and PR positive patients, where only 7.1% showed response to progesterone treatment in ER positive group.[28] We reported a longer cumulative survival rate in ER and PR positive patients, compared to the patients without it and Liao et al. reported similar results (Fig. 1).[25]

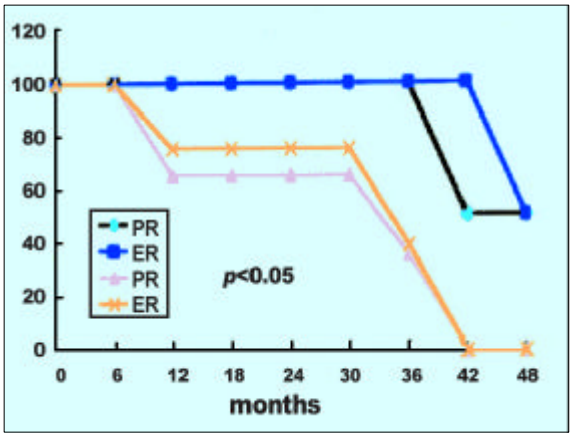


Fig. 1. Cumulative survival according to ER and PR status.

DNA flow-cytometric analysis and karyotyping

About one-third of endometrial cancer have aneuploid DNA content, and its association with poor histologic grade and poor prognosis has been confirmed in limited studies. Iverson reported positive correlation between aneuploidy, recurrence rate, and mortality rate.[29] On the other hand, Geisinger et al. reported comparatively deeper myometrial invasion in patients with diploidy, therefore the above mentioned positive correlation could not be approved.[26] Without universal consensus, the mortality rate is said to increase in aneuploidy. Stendahl et al. reported a poor prognosis in patients with high s-phase fraction.[30] The proliferative index has been demonstrated to be a better prognostic parameter compared to tumor ploidy status, but the flow cytometric analysis still encompasses problems in the size of study population, study method, and interpretation which lacks objectivity and reproducibility; clinical application still faces problems. The results of karyotyping demonstrated trisomy or tetrasomy in the long arm of chromosome 1 as the most common abnormality, but further studies are warranted for karyotyping to be used in clinical practice.

Tumor markers

Limited studies have undergone about tumor markers of endometrial cancer. In 50% of endometrial cancers, elevation of serum CA-125, CA19-9, and basic fetoprotein (BFP) was demonstrated.[31] Duk et al. reported CA-125 elevation in 25% endometrial cancers, and increased level of CA-125 was noted with advancing stage.[32] The CA-125 level might be used in early diagnosis of recurred endometrial cancer, but its correlation with prognosis lacks prospective study.

Oncogene and tumor suppressor gene

Ras oncogene

Ras oncogene is a proven proto-oncogene in human activated by point mutation. The three ras oncogene, H-ras, K-ras, and N-ras, share a common amino acid sequence, with a subtle difference in c-terminal. The point mutation in codon 12 of ras-oncogene changes glycine to other amino acid except proline, and this transformation results in tumorigenesis. The p-21 ras has high affinity with GDP and GPT, and activates GTPase. Fujimoto et al. reported a 22.2% K-ras point mutation rate, and this abnormality was associated with high rate in lymph node metastasis.[33] Mizucchi et al. reported K-ras point mutation as a poor prognostic parameter in endometrial cancer.[34]

c-erbB-2 oncogene

In the uterine cavity exposed by ethyl nitrosourea, c-erbB-2 oncogene activates to cause neuroblastoma; c-erbB-2 was initially named as the neu oncogene by Padhy et al.[35] Initially c-erbB-2 oncogene was demonstrated by many researchers as her-2 or neu oncogene, and it was said to synthesize polypeptide growth factor receptor or proteins similar to growth factor receptors. The proteins encoded by c-erbB-2 oncogene shows 88% similarity with the epidermal growth factor receptor encoded by c-erbB-1 oncogene. Czerwenka et al. reported 72 endometrial cancer patients where no correlation between overexpression of c-erbB-2 and poor prognosis was found.[36] In contrast to that, Saffari et al. reported the overexpression of c-erbB-2 as an independent prognostic parameter.[37] In our institution though enzyme immunoassay, c-erbB-2 oncogene expression in relation to tumor stage was studied; positive correlation between c-erbB-2 oncogene expression with advanced stage was noted but it did not show a statistic significance. The discrepancies in many studies of c-erbB-2 oncogene are due to variable study methods and inconclusively determined mean values.

c-myc oncogene

c-myc oncogene was isolated in avian MC-29 retrovirus in 1980. It regulates the 62kd transcriptional factor, which facilitates G0 phase of cell cycle to G1 phase. In human, c-myc oncogene is located on chromosome 8; the overexpression and amplification can be considered as a prognostic parameter. In endometrial cancer, 10% to 20% over-expression of c-myc oncogene and 30% to 60% amplification was demonstrated. In our study with PCR-Southern blotting, 26% of endometrial cancer patients showed c-myc-oncogene amplification, and the rate increased in poor histologic grades (Fig. 2).

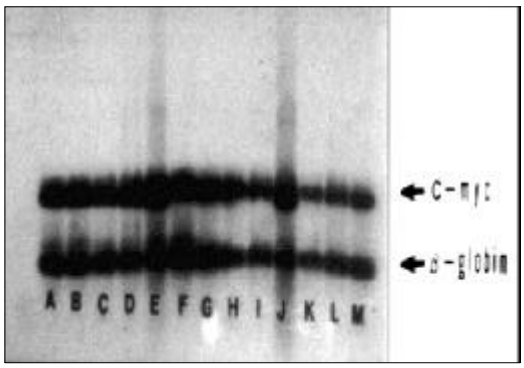
p53 tumor suppressor gene

The allelic loss or mutation of p53 tumor suppressor gene located on the long arm of chromosome 17, is one of the common abnormality associated with prognosis. In endometrial cancer, p53 overexpression is reported in 20%, and it shows a positive correlation with advanced stage and papillary serous carcinoma which can be considered as a poor prognostic factor.[38,39] Pisani et al. reported a higher cumulative survival rate in patients without p53 overexpression compared to patients without it.[40] Table 3 and Fig. 3 show our study result that p53 overexpression has positive correlation only with tumor grade.

Apoptosis related proteins

Bcl-2

Bcl-2 is an oncogene located on chromosome 18,



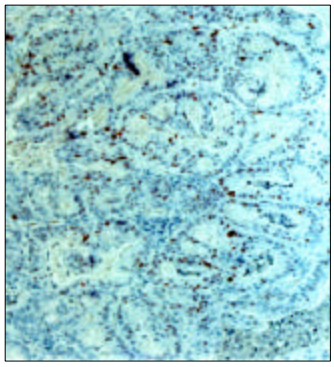
Grade	No	+	-
I	12	1(8.3%)	11
II	5	2(40%)	3
III	4	3(75%)	1

p=0.02 (I,II vs. III)

Fig. 2. Correlation between c-myc gene amplification and grade (Unpublished data, YUMC, 1999).

Table 3. Relationship between p53 Overexpression and Various Clinicopathologic Prognostic Factors

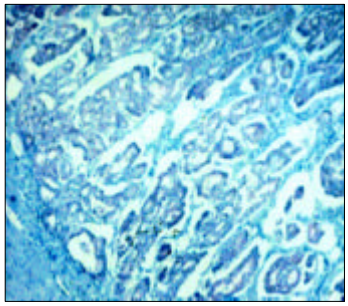
	p53 overexpression		p value
	Present	Absent	
FIGO stage			0.198
I/II	8	18	
III/IV	4	3	
Grade			0.005
Well-differentiated	2	17	
Moderately-differentiated	7	4	
Poorly-differentiated	3	0	
LN metastasis			0.222
No	4	12	
Yes	2	1	
Myometrial invasion			0.154
None	2	8	
Less than 1/2	4	9	
More than 1/2	6	4	
Cell type			0.457
Endometrioid	9	19	
Non-endometrioid	3	2	



Grade	No	+	-
I	19	2(10.5%)	17
II	11	7(63.6%)	4
III	3	3(100%)	0

p=0.005

Fig. 3. Correlation between p53 expression and grade.



Bax expression: 19/33(57.6%)

Factors	p value
Surgical stage	0.04
Grade	NS
Histological cell type	NS
Myoinvasion	NS
Lymph node metastasis	NS
ER, PR positivity	NS

Fig. 4. Correlation between Bax expression and clinicopathological factors (Unpublished data, YUMC, 1999)

which plays a role in prolonging cell survival by preventing apoptosis. According to Saegusa et al., Bcl-2 expression in endometrial cancer has been reported to be correlated with stage, grade, and myometrial invasion.[41] Taskin et al. also reported a strong correlation of Bcl-2 expression with stage, grade, and PR positivity.[42] However, there was no correlation between Bcl-2 expression and clinicopathological factors in the study of Chhieng et al.[43] and Miturski et al.[44] In our study as well, no correlation of Bcl-2 expression with any of the clinicopathologic factors was found.

Bax

Bax is a pro-apoptotic member of Bcl-2 family of genes, which regulate programmed cell death. Its expression is elevated after apoptotic stimuli and can be directly regulated by p53. We have studied the correlation between Bax expression and clinicopathologial factors. About 58% of endometrial cancer patients showed Bax expression and it was correlated with surgical stage only (Fig. 4).

Cell cycle related antigens

Cell kinetic information is becoming a valuable prognostic parameter in endometrial cancer. The PCNA (proliferating cell nuclear antigen) is an auxiliary protein of DNA polymerase associated with the late G1 phase and s-phases of the cell cycle, exhibiting a proliferative activity. Garzetti et al. reported a higher recurrence rate in patients with a higher PCNA index; in 12 patients with PCNA index higher than 50%, 5 patients recurred, but only 1 patient out of 62 patients with PCNA index lower than 50% recurred.[45] Sasano et al. reported the PCNA to be a discriminating factor between endometrial hyperplasia and cancer, but further studies are warranted to establish its role.[46] Gerdes et al. reported Ki67, silver-staining nuclear organizer regions (AgNORs), and DNA polymerase α as other cell cycle related antigens.[47]

Cyclins govern the cell cycle progression through checkpoints, mediating their action by activation of cyclin dependent kinase. The G1/S phase transition is mediated by cyclin C, D,[48] and E, while the G2/M phase transition is mediated by cyclin A and B. Using the slot blotting method, 81% of cyclin D1 m-RNA expression was demon-

Table 4. Expression of E-cadherin, Catenins, and Vinculin in Endometrial Cancer

	Number	Normal	Aberrant
E-cadherin	33	21 (63%)	12 (37%)
Catenin			
α	33	24 (73%)	9 (27%)
β	33	27 (82%)	6 (18%)
γ	33	16 (49%)	17 (51%)
Vinculin	33	10 (30%)	23 (70%)

Aberrant includes heterogenous and negative staining.

strated, while using the immunohistochemistry, 30% showed cyclin D1 expression. Although some authors reported correlation between cyclin D1 and poor prognosis, in our study, no correlation with any of clinicopathological factors was found.

Another category of cell cycle-related protein is CDK inhibitor such as $p21^{WAF1/CIP1}$. $p21^{WAF1/CIP1}$ inactivates cyclin E-CDK2 and cyclin D-CDK4, inhibits DNA replication by interacting with PCNA, and prevents cells entering S-phase. There have been controversial reports on the expression of $p21^{WAF1/CIP1}$. Ito et al. has reported a better prognosis in patients with $p21^{WAF1/CIP1}$ expression,[49] but in our study and that of Backe et al.'s[50] no correlation of $p21^{WAF1/CIP1}$ expression with clinicopathological factors and survival were demonstrated.

Molecules associated with stromal invasion and metastasis

The stromal invasion and metastasis of cancer is undoubtedly associated with prognosis, and this is also observed in endometrial cancer (Table 4). Vogel et al. reported a progressive loss of laminin, which is one of the basement components, in poor tumor grades.[51] Cathepsin D, a proteolytic enzyme, is reported to be related with breast cancer metastasis, and Maudelonde et al. reported a positive correlation between myometrial invasion and Cathepsin D in endometrial cancer.[52] A decrease in E-cadherin, expression which is an extracellular matrix protein, was associated with increased invasive behavior of the cancer; Inoue et al. reported a decreased expression of E-cadherin in poorly differentiated endometrial cancer,[53] but in a practical standpoint, further study results are required.

CONCLUSIONS

Many studies are presently in progress to investigate valuable prognostic parameters of endometrial cancer. Prognostic parameters enable the practitioner to choose the best treatment modality for the prevention of recurrence. The clinicopathologic prognostic parameters and the newly investigated biologic prognostic parameters accommodate us with the added ability to anticipate the patients' prognosis. But most of the studies are done with a small study population in a retrograde method, and only demonstrates the association of the proposed prognostic parameters with survival rate. Further studies are warranted in investigating the prognostic parameters, and the practitioner should choose the most appropriate treatment modality according to the individual's need.

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