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Original Research

P53 overexpression predicts unfavorable prognosis of low risk endometrial carcinoma

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Summary

Aim: Mutations of PTEN, p53 are the most frequent molecular defects in endometrial carcinomas (EC). Aim of this study was to investigate their prognostic significance in EC, especially for low risk EC. *Materials and Methods:* This retrospective study included 99 patients with diagnosed endometrial adenocarcinoma. Paraffin embedded specimens were studied immunohistochemically for detection of PTEN, p53 proteins. Correlation of p53 overexpression and loss expression of PTEN with several well-established prognostic parameters and survival rate were evaluated. *Result:* Overexpression of p53 was an independent prognostic factor for EC. Stratified analysis showed that p53 overexpression was a significant prognostic factor for low-grade ($p < 0.0001$), early -stage ($p < 0.0001$), EC (< 0.0001), and non-nodal metastasis ones, but not for high-grade ($p = 0.080$), type II EC ($p = 0.056$), advanced EC ($p = 0.632$) or nodal metastasis ones ($p = 0.660$). The present study failed to demonstrate that loss expression of PTEN was correlated with survival rate of EC. *Conclusion:* p53 overexpression was an independent prognostic factor of EC, especially for low-grade, early-stage, EC and non-nodal metastasis ones. Loss expression of PTEN was not correlated with survival rate of EC.

Key words: p53; PTEN; Endometrial carcinoma; Immunohistochemistry; Prognosis

Introduction

Endometrial carcinoma (EC) is a common malignancy of the gynecologic tract and ranks fourth in incidence among invasive tumors for women in North America and Europe, and the prevalence is still increasing [1]. Pathologically, EC are divided into two types: type I, estrogen-dependent tumors associated with adenomatous hyperplasia. The majority (75%) are diagnosed in early stage and cured by surgery. Type II are estrogen-independent, with poor prognosis. The most frequent molecular defects in type I carcinomas are mutations of PTEN, k-ras, β-catenin genes, and microsatellite instability, whereas type II often exhibits mutations of p53 and loss of heterozygosity located on certain chromosomes [2, 3].

There are diverging results in correlation between p53 overexpression, loss expression of PTEN, and outcome of EC. The majority presume that p53 overexpression associated with adverse outcome of EC, and loss expression of PTEN associated with poor prognosis of advanced stage EC [4-8]. The aim of this study was to investigate the expression of PTEN, p53 proteins in EC, and evaluate correlation of p53, PTEN with well-established prognostic parameters, including survival rate to find their prognostic significance.

Prognosis of early stage of EC is relatively better than most other types of cancer. However in clinical practice, heterogeneity of patients's characteristics in early-stage EC were observed [9]. Recurrence of early-stage EC was demonstrated to be 15–20% [10, 11]. European Society for Medical Oncology (EMSO) established three risk groups with regards to depth of myometrial invasion, histological grade, and type to evaluate risk of recurrence of early stage of EC, which will help to provide indications for adjuvant therapies [11, 12]. Detailed risk groups are as follows: low risk (type 1 EC, Stage IA, Grade 1 or 2); intermediate risk (type 1 EC, Stage IA, Grade 3, or Stage IB, Grade 1 or 2), and high risk (type 1 EC, Stage IB Grade 3, or type 2 EC of any stage and grade). To further investigate the importance of p53 and PTEN in low risk group, the authors conducted stratified analysis, revealed that p53 overexpression was a significant prognostic factor for low-grade ($p < 0.0001$), early stage ($p < 0.0001$) , and EC ($p < 0.0001$) (Figure 1), and non-nodal metastasis ones. In the future, p53 may help to establish more accurate risk stratification system, and improve survival of patients with EC, especially those in early stages.

Materials and Methods

Total of 99 cases were retrieved from the Department of Pathology in West China Second University Hospital, Sichuan University from year of 1996 to 2007. Their median age was 53. 92 years (range, 32-75 years). Samples were all from hysterectomy specimens. None of the patients with endometrial carcinoma received chemotherapy or radiotherapy before surgery, which consisted of peritoneal cytology, total hysterectomy, bilateral salpingo-

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Table 1. — *Clinicopathologic characteristics of 99 patients with endometrial carcinomas.*

Characteristics	Frequency	Percentage (%)
Total	99	100.0
Histology		
Type I	73	73.7
Type II	26	26.3
Stage		
I	50	50.5
II	9	9.1
III	33	33.3
IV	7	7.1
Grade (n=73)		
G1	25	25.3
G2	7	7.1
G3	41	41.4
Lymph node		
Positive	29	29.3
Negative	52	52.6

Table 2. — *Clinical outcome of three year survival rate.*

Variable	dead	alive	withdraw	p
Total (n=99)	35 (35%)	57 (58%)	7 (7%)	
Histology				
Type I	21 (29%)	47 (64%)	5 (7%)	0.017
Type II	14 (54%)	10 (38%)	2 (8%)	
Stage				<0.0001
I+II	10 (17%)	44 (75%)	5 (8%)	
III+IV	25 (63%)	13 (33%)	2 (4%)	
Grade				0.010
1+2	5 (16%)	27 (84%)	0 (0%)	
3	16 (39%)	20 (49%)	5 (12%)	
Lymph node				0.001
Positive	18 (62%)	10 (34%)	1 (4%)	
Negative	17 (24%)	47 (67%)	6 (9%)	
p53				0.004
+	10 (64%)	3 (18%)	3 (18%)	
-	25 (30%)	54 (65%)	4 (5%)	
PTEN				0.660
+	17 (35%)	25 (51%)	7 (14%)	
-	18 (36%)	32 (64%)	0 (0%)	

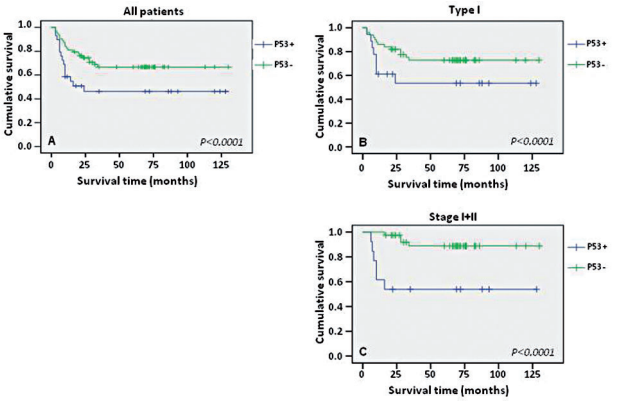

Figure 1. — Kaplan-Meier survival curves according to p53 expression for patients with endometrial carcinoma. (A) Log-rank test reveals that p53 overexpression correlated significantly with worse outcome for all patients ($p < 0.0001$). (B, C) Stratified Log-Rank analysis for Type I and Stage I+II patients, revealing p53 overexpression predicts worse outcome ($p < 0.0001$).

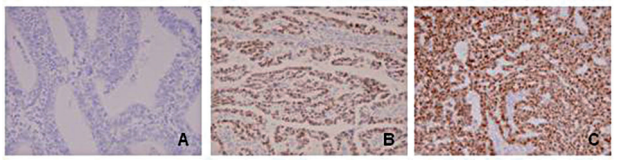

Figure 2. — Immunohistochemistry of p53. (A) Negative p53 overexpression (G1). (B) Moderate p53 overexpression (G2). (C) Intense p53 overexpression (G3).

oophorectomy, and pelvic and para-aortic lymph node sampling when necessary. In accordance with International Federation of Gynecologists and Obstetricians (FIGO) recommendations, women with Stage I Grade 1 EC did not undergo lymphadenectomy. The authors adopted the histologic features described by the World Health Organization and staged disease according to the International Federation of Gynecology and Obstetrics (FIGO) system.

Two pathologists reviewed all the tissue samples to confirm the diagnosis and histological characteristics. Written informed consent was obtained from patients or their legal surrogates prior to enrolment. The study protocol was approved by the Clinical Research Ethics Committee of the West China Second University Hospital.

Paraffin-embedded sections (4 μm) were cut and prepared on adhesive slides. Briefly, the authors used mouse anti-human p53 monoclonal antibody (clone DO-7, isotype IgG2b, 1:50, mouse anti-human PTEN monoclonal antibody clone DO-7, isotype IgG1, 1:100). Positive controls were sections of breast cancer. For negative controls the primary antibody was replaced by an irrelevant non-immune mouse antibody of the same IgG subtype.

Immunoreaction of endometrial tumor cells was assessed semiquantitatively. For semiquantitative analysis, the percentage of positive cells was counted for approximately 1,000 neoplastic cells per slide, subdivided into ten selected fields at ×400 magnification (Figure 2). Immunostaining was assessed by two independent Observers, blinded for patient's clinicopathologic and outcome data. The mean of two observations was used for analysis. Only nuclear staining was considered positive for both p53 and PTEN. Percentage of 50% was the cut-off value for both p53 and PTEN.

In this study "+" indicated p53 overexpression or loss expression of PTEN, while "-" indicated no p53 overexpression or loss expression of PTEN.

Statistical analysis and graphs were performed applying SPSS software package version 17. 0. Survival curves were constructed with the use of the Kaplan–Meier method, and compared using the log-rank test. Multivariate analysis was performed with the use of Cox's proportional hazard models ($p < 0.05$).

Table 3. — *Results of χ^2 analysis showing the correlations between p53 overexpression and clinicopathologic parameters.*

Variable	N	p53 over expression		*p*
		+(%)	-(%)	
Histology				0.083
Type I	73	9 (12%)	64 (88%)	
Type II	26	7 (27%)	19 (73%)	
Stage				0.028
I	50	5 (10%)	45 (90%)	
II	9	1 (11%)	8 (89%)	
III	33	6 (18%)	27 (82%)	
IV	7	4 (57%)	3 (43%)	
Grade				0.068
1+2	32	1 (3%)	31 (97%)	
3	41	8 (20%)	33 (80%)	
Lymph node				0.186
Positive	29	8 (28%)	21 (72%)	
Negative	52	8 (15%)	44 (85%)	

Table 4. — *Log-rank test for p53 overexpression +/- of three-year survival rate.*

Variables	p53 overexpression (dead)		*p*
	+(%)	-(%)	
Total (n=92)	10/13 (77%)	25/79 (32%)	<0.0001
Type I	5/7 (71%)	16/61 (26%)	<0.0001
Type II	5/6 (83%)	9/18 (50%)	0.056
I+II	4/4 (100%)	6/50 (12%)	<0.0001
III+IV	6/9 (67%)	19/29 (66%)	0.623
G1+G2	1/1 (100%)	4/31 (13%)	<0.0001
G3	4/6 (67%)	12/30 (40%)	0.080
Lymph node (+)	4/7 (57%)	14/21 (67%)	0.660
Lymph node (-)	6/6 (100%)	11/40 (28%)	<0.0001

Table 5. — *Results of χ^2 analysis showing the correlations between loss expression of PTEN and clinicopathologic parameters.*

Variables	N	loss expression of PTEN		*p*
		+N (%)	-N (%)	
Histology				0.153
Type I	73	33 (45%)	40 (55%)	
Type II	26	16 (62%)	10 (38%)	
Stage				0.045
I	50	19 (38%)	31 (62%)	
II	9	4 (44%)	5 (56%)	
III	33	20 (61%)	13 (39%)	
IV	7	6 (86%)	1 (14%)	
Grade				<0.0001
1+2	32	7 (22%)	25 (78%)	
3	41	26 (63%)	24 (47%)	
Lymph node				0.678
Positive	29	17 (59%)	12 (41%)	
Negative	52	28 (53%)	24 (47%)	
p53				0.965
+	16	8 (50%)	8 (50%)	
-	83	41 (49%)	42 (51%)	

Table 6. — *Log-rank analysis for PTEN loss expression +/- of three year survival rate.*

Variables	Loss of expression of PTEN (dead)		*p*
	+N (%)	-N (%)	
Total (n=99)	17/42 (40%)	18/50 (36%)	0.522
Type I	8/28 (29%)	13/40 (32%)	0.823
Type II	9/14 (64%)	5/10 (50%)	0.395
I+II	1/18 (6%)	9/36 (25%)	0.198
III+IV	16/24 (67%)	9/14 (64%)	0.630
G1+G2	0/7 (0%)	5/25 (20%)	0.198
G3	8/21 (38%)	8/15 (53%)	0.504
Lymph node (+)	10/16 (63%)	8/12 (67%)	0.974
Lymph node (-)	7/22 (32%)	10/24 (42%)	0.574

Results

There were 73 endometrioid (type I) and 26 non-endometrioid (type II) carcinomas. The latter comprised of 16 serous carcinomas, seven mixed EC, two squamous cell EC, and one mucinous EC. Fifty tumors were Stage I, nine were Stage II, 33 were Stage III, and seven were Stage IV. Thirteen, 25, and 42 tumors for FIGO Grades 1, 2, and 3, respectively. Lymph node involvement at the time of surgery was found in 29 patients. Eighteen patients did not undergo lymphadenectomy with Stage I, Grade 1 EC. In this study, 35 of the patients died, 57 were alive, and seven were withdrawal. The clinical and histological characteristics are summarized in Table 1.

Follow-up was from three to 130 months. The onset and termination of follow up were surgery date and 2008-12-31. Thirty–five patients died, 57 were alive, and seven were withdrawal. In total three-year survival rate was 60%. Twenty-one (29%) endometrioid EC patients died, 14 (54%) non-endometrioid EC patients died (Table 2).

p53 overexpression was only significantly correlated with increased stage ($p = 0.028$), but p53 overexpression was increasingly found in non-endometrioid EC, Grade 3, positive lymph nodes compared to endometrioid EC, Grade 1 + Grade 2, lymph nodes negative ones. The correlation between p53 overexpression and survival rate of EC patients are shown in Table 3.

In this study, p53 positive overexpression was correlated with a significantly worse outcome ($p < 0.0001$) (Table 2). In endometrioid EC, patients with p53 positive overexpression showed worse outcome ($p < 0.0001$), while in non endometrioid EC, there was no significant survival rate difference between p53 overexpression positive and negative ones ($p = 0.056$). In Stage I+II EC, patients with p53 positive overexpression showed worse outcome ($p < 0.0001$), while in Stage III+IV EC, there was no significant survival rate difference between p53 overexprestion positive and negative ones ($p = 0.623$). In Grade 1+Grade 2 EC, patients with p53 positive overexpression showed worse outcome ($p < 0.0001$), while in Grade 3 EC, there was no significant survival rate difference between p53 overexpression positive and negative ones ($p = 0.080$). In lymph nodes(-) EC, patients with p53 positive overexpression

showed worse outcome ($p < 0.0001$), while in lymph nodes (+) EC, there was no significant survival rate difference between p53 overexpression positive and negative ones ($p = 0.660$) (Table 4). In univariate analysis, a shorter survival was strongly associated with increased stage ($p < 0.0001$) and a positive nodal status ($p < 0.0001$) as well as with a non-endometrioid histology ($p = 0.002$) and low differentiation ($p = 0.03$) (Table 2).

In multivariate analysis (Cox regression analysis), including all parameters studied, revealed that only p53 overexpression ($p = 0.021$) and Stage ($p = 0.012$) had independent impact on survival.

Correlation analysis revealed that loss expression of PTEN correlated with increased stage and worse differentiation (Table 5). Loss expression of PTEN was significantly correlated with increased stage ($p = 0.045$) and poor differentiation ($p < 0.0001$) (Table 2). There was no significant correlation between p53 overexpression and loss expression of PTEN ($p = 0.965$).There was no significant correlation between loss expression of PTEN and survival rate of EC patients (Table 6).

Discussion

EC is a common gynecologic malignancy and the death rate has increased over 100% during the past two decades [13]. It is well certificated that the most important prognostic factors of EC are advanced surgical stage, poorly differentiated histologic grade, non-endometrioid histologic subtype, deep myometrial invasion, and presence of lymphovascular invasion. The present study also proved the point. However, for low and intermediate risk groups there is still a certain recurrence rate, and then more specific prognostic markers are needed to give reasonable adjunctive treatment to invasive ones of low and intermediate risk groups. Recently many molecular prognosis factors were studied, such as p53, PTEN, bcl-2, MDM2, COX-2 [14, 15]. P53 overexpression and loss expression of PTEN demonstrated to be prognostic markers for EC, but their prognostic value for low and intermediate risk group has still not been investigated.

P53 serves as a genome guardian. It functions mainly as a transcription factor by binding to specific DNA sequences to transfer a large group of target genes. P53 regulates the pathways of cell-cycle arrest, apoptosis, and DNA repair, maintaining a dynamic equilibrium among cell growth, arrest, and death under stressful conditions, such as DNA damage, hypoxia, deficiency of nutrients, etc [16]. Half life period of wild p53 protein is too short to be detected in cells by normal method, while mutated p53 protein shows increased half life period to accumulate in nuclear so that it can be detected by immunohistochemistry.

In previous studies, p53 overexpression showed significant correlation between advanced stage, poor grade of differentiation, non-endometrioid EC, deeper myometrial invasion, and lymph nodes positive. In the present study p53 overexpression was only significantly correlated with increased stage ($p = 0.028$), and p53 overexpression was increasingly found in non-endometrioid EC, G3, positive lymph nodes compared to endometrioid EC, Grade 1+Grade 2, negative lymph nodes.

In this study, p53 overexpression was correlated with a significantly worse outcome in endometrioid, Stage I+II, Grade 1+Grade 2, negative lymph nodes EC (all, $p < 0.0001$). While in non-endometrioid, Stage III+IV, Grade 3, positive lymph nodes EC, there was no significant survival rate difference between positive and negative p53 overexpression (Table 4). In multivariate analysis (Cox regression analysis) revealed that P53 overexpression ($p = 0.021$) and stage ($p = 0.012$) were independent prognostic factors. p53 overexpression is a useful prognostic factor for relatively low risk group, endometrioid, Stage I+II, Grade 1+Grade 2, negative lymph nodes EC.

To further validate the correlation between p53 overexpression and outcome of EC, efforts should be made to unify the cutoff value. In previous studies, variant cutoff values were adopted, such as 5%, 10%, 50%, and 80% [17, 20]. When p53 overexpression was used in diagnosis, low cutoff value improved the sensitivity, on the other hand, when p53 overexpression was used in judging prognosis, high cutoff value improved the specificity. So when choose cutoff value the usage should be taken into consideration.

The present study manifested that p53 overexpression in non-endometrioid EC was 27%, lower than 68%-100% ever reported in other studies [21]. This is probably because the cutoff value was higher than the ones in other studies.

PTEN mutation is the most frequent genetic alteration in endometrioid EC. PTEN mutations have been also found in precancer lesions such as complex atypical endometrial hyperplasia or Endometrial Intraepithelial Neoplasia. There is both clinical and experimental evidence that PTEN alteration is an early event of EC and p53 mutation is a late event. There was diverging on the correlation between loss expression of PTEN and prognosis of EC [22, 23].

Accordance with the previous reports, loss expression of PTEN in this study was associated with increased grade and advanced stage [7]. Indicating that in early stage or well differentiated tumors some PTEN still could play role in cancer suppressing, along with continuous loss expression of PTEN its anti-cancer effect is impaired and cancer becomes more invasive.

Erkanli *et al.* showed mean survival was statistically significantly higher in PTEN-positive cases ($p = 0.05$) [24]. The same results were found in some other studies, indicating that patients with loss expression of PTEN had shorter survival [25]. Converse results concluded in some reports that patients with loss expression of PTEN had a better outcome [26]. The present study showed that loss expression of PTEN did not correlate with survival rate of EC. Though PTEN plays an important role in carcinogen-

esis of endometrioid EC and, as a tumor suppressor gene, it seems more reasonable that loss expression of PTEN correlates with worse outcome and it may not be an ideal prognostic factor, like p53 to endometrioid EC.

Conclusion

p53 overexpression was an independent prognostic factor of EC, especially for low-grade, early-stage, EC and non-nodal metastasis ones, but not for Grade 3 or type II EC. This study indicated that loss of expression of PTEN was not correlated with survival rate of EC, but was significantly correlated with advanced stage and high-grade tumor differentiation.

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