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Loss of PTEN expression is an independent predictor of favourable survival in endometrial carcinomas

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Background: We and others previously reported the prognostic significance of *PTEN* mutational status on favourable survival in endometrial carcinomas. Here, we demonstrate that loss of PTEN expression in immunohistochemistry is an independent prognostic marker for favourable survival in endometrial carcinomas.

Methods: We conducted immunohistochemical analyses of PTEN, PIK3CA, phosphorylated Akt (p-Akt), and p27 in primary endometrial carcinomas from 221 patients. Mutation of PTEN was analysed further.

Results: Expression of PTEN was lost in 56 patients (25%), and PIK3CA was overexpressed in 159 patients (72%). Overexpression of PIK3CA was associated with p-Akt overexpression ($P<0.001$), which was in turn associated with loss of nuclear p27 expression ($P=0.028$). Loss of PTEN expression was found to be associated with endometrioid histology ($P=0.03$), and was inversely associated with the presence of lymphovascular space invasion ($P=0.03$). Univariate and multivariate survival analyses revealed that factors of PTEN loss, age <70, histological grade 1, early International Federation of Gynecology and Obstetrics (FIGO) stage, and absence of lymphovascular invasion were independent prognostic indicators for better overall survival ($P=0.03$, 0.04, 0.01, <0.001, and 0.03, respectively). The subset analysis showed a stronger tendency of PTEN loss towards favourable survival in advanced-stage (III and IV) disease than in early-stage (I and II) disease ($P=0.05$ *vs* 0.14). Moreover, our mutational analysis demonstrated that PTEN expression loss was associated with PTEN-truncating mutations ($P=0.03$).

Conclusion: The current observations further support the prognostic significance of *PTEN* aberration on favourable outcome in endometrial carcinomas, providing useful implications for the individualised management of the disease.

Dysregulated signalling on the phosphatidylinositol 3' (PI3)-kinase/PTEN/Akt cascade is reported to be associated with early-stage disease and favourable prognosis in some types of malignancy, including colon, breast, ovarian, and endometrial cancers. Regarding breast cancer, it has been reported that PIK3CA mutation is associated with positive oestrogen receptor status, low stage, and favourable outcome (Kalinsky *et al*, 2009). In colorectal cancer, Baba *et al* (2011) have reported that phosphorylated Akt (p-Akt) expression is associated with PIK3CA mutation, low stage, and favourable outcome. In ovarian cancer, we and others have recently reported that PIK3CA aberration is associated with favourable survival in ovarian clear cell carcinoma (Rahman *et al*, 2012; Abe *et al*, 2013). As for endometrial cancer, we and others previously reported that PTEN mutation is associated with endometrioid histology, early stage, and favourable prognosis (Risinger *et al*, 1998; Minaguchi *et al*, 2001). The current study has aimed to investigate the prognostic significance of immunohistochemical (IHC) PTEN expression in endometrial carcinoma. Here,

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we demonstrate that loss of PTEN expression is a significant and independent prognostic factor for favourable survival in the disease. Our observation presents additional evidence for the prognostic significance of *PTEN* aberration on favourable outcome in endometrial carcinoma, further providing significant implications for the management of the disease including molecular targeted therapies.

MATERIALS AND METHODS

Patients and specimens. The Ethical Committee of the University of Tsukuba Hospital approved the study protocol. All patients diagnosed with endometrial carcinoma, who were treated in the Department of Obstetrics and Gynecology at the University of Tsukuba Hospital between 1999 and 2009, were identified through our database. A total of 221 patients with endometrial carcinomas were included in the present study, and their medical records were reviewed. A median follow-up duration was 59 months (range, 3–119 months). All patients provided written informed consent. Staging was performed based on the criteria of International Federation of Gynecology and Obstetrics (FIGO). Endometrioid adenocarcinomas were subclassified into three grades (G_1, G_2, and G_3) according to the FIGO criteria. Table 1 summarises the patient characteristics.

Treatment. The operative procedure included hysterectomy, bilateral salpingo-oophorectomy, and systematic aortic and pelvic lymph-node dissection. Radical hysterectomy or semiradical hysterectomy (with removal of vaginal cuff and partial resection of vesico-uterine ligament) was performed on patients with positive findings on cervical stromal invasion by MRI, and simple total hysterectomy was performed on the remainder. Postsurgically, patients with positive peritoneal cytology, adnexal/peritoneal involvement, or pelvic-/aortic-node metastases were treated with combination chemotherapy of paclitaxel and carboplatin. Small-pelvis irradiation (with the lower superior border of field) was indicated for patients with adnexal/peritoneal involvement or deep muscular invasion (more than two-thirds depth in endometrioid $G_{1,2}$ and more than one-half in G_3 or other histotypes). Whole-pelvis or periaortic irradiations were administered to pelvic or aortic node-positive patients, respectively.

Immunohistochemistry. Immunohistochemistry was performed as described previously (Abe *et al*, 2013). Antibodies used were PI3 Kinase p110α (rabbit monoclonal, 1 : 200; Cell Signaling, Danvers, MA, USA), Anti-Human PTEN (6H2.1) (mouse monoclonal, 1 : 100; Cascade, Winchester, MA, USA), Phospho-Akt (Ser473) (rabbit monoclonal, 1 : 50; Cell Signaling), and Anti-p27 (mouse monoclonal, 1 : 100; BD Pharmingen, Franklin Lakes, NJ, USA). The corresponding normal endometria or stroma provided an internal positive control, and negative controls without addition of primary antibody showed low background staining.

IHC scoring. For semiquantitative analyses, the IHC staining was scored by multiplying the percentages of positive tumour cells (PP: 0, no positive cell; 1, <10%; 2, 10–50%; and 3, >50% positive tumour cells) by their prevalent degree of staining (SI: 0, negative; 1, decreased; 2, equivalent; and 3, increased staining to the corresponding normal tissue). The IHC scores (IHS = PP × SI) range from 0 to 9. The average value from the scores of two independent observers (AA and TM) blinded for clinicopathological parameters was used as the final value. For the evaluation of PTEN expression, IHS = 0 was considered as negative. For PIK3CA and p-Akt, IHS > 6 was evaluated as overexpression. For p27, no staining of tumour cell nuclei was evaluated as nuclear negative. Figure 1 shows examples of IHC staining patterns in normal endometria and endometrial carcinomas. For normal control, normal endometria from 15 women were examined, and >90% of the specimens were scored as 6 for PTEN, p-Akt, and PIK3CA, and >85% were positive for p27, respectively.

Table 1. Patient characteristics

Characteristic	Number $n = 221$
Median age (range)	57.0 (26–84)
FIGO stage	
I	128
Ia	22
Ib	76
Ic	30
II	26
IIa	10
IIb	16
III	43
IIIa	20
IIIc	23
IV	24
IVa	2
IVb	22
Histotype	
Endometrioid	196
G_1	115
G_2	56
G_3	25
Serous	12
Adenosquamous	4
Clear cell	4
Poorly differentiated	1
Undifferentiated	1
Mixed epithelial	3
Primary treatment	
Surgery	221
Lymphadenectomy	171
Lymph-node sampling	21
Chemotherapy	60
TC	55
CAP	4
Irradiation	58

Abbreviations: CAP = cyclophosphamide, doxorubicin, and cisplatin combination; FIGO = International Federation of Gynecology and Obstetrics; TC = paclitaxel and carboplatin combination.

DNA extraction and PTEN mutational analysis. Genomic DNA was extracted from tumour areas of formalin-fixed, paraffin-embedded archival tissues with a Dneasy Blood & Tissue Kit (Qiagen, Valencia, CA, USA) according to the manufacturer's instructions. Mutational analysis for *PTEN* was performed as previously described. Briefly, aberrant bands revealed by SSCP analysis were excised from the gel, amplified by PCR, purified, and submitted to the Operon Biotechnologies (Tokyo, Japan) for direct sequencing.

Statistical analysis. Differences in proportions were evaluated by the Fisher's exact test. Kaplan–Meier survival curves were calculated and compared statistically using the log-rank test.

The Cox proportional hazard model was used for the univariate and multivariate analyses.

RESULTS

Our IHC analyses in 221 endometrial carcinomas showed that PTEN expression was lost in 56 cases (25%), PIK3CA was overexpressed in 159 (72%), p-Akt was overexpressed in 189 (86%), and nuclear p27 expression was lost in 143 (65%) (Table 2). Moreover, overexpressed PIK3CA was significantly associated with p-Akt overexpression ($P<0.001$), which in turn significantly correlated with negative nuclear p27 expression ($P=0.03$) (Table 2). These observations are consistent with the signal transduction mechanism where upregulation of PI3 kinase leads to phosphorylation of Akt, which in turn results in translocation of p27 from nucleus to cytoplasm. This consistency strengthens the validity of our IHC analyses.

We subsequently investigated the relationships between IHC results and clinicopathological parameters (Table 3). Loss of PTEN expression was found to be associated with endometrioid histology ($P=0.03$), and was inversely associated with the presence of lymphovascular invasion ($P=0.03$). Negative nuclear p27 expression was associated both with endometrioid histology and with G_1 ($P=0.008$ and 0.016, respectively). Negative PTEN showed trends towards younger age ($P=0.10$), obesity ($P=0.17$), and less lymph-node metastases (data not shown).

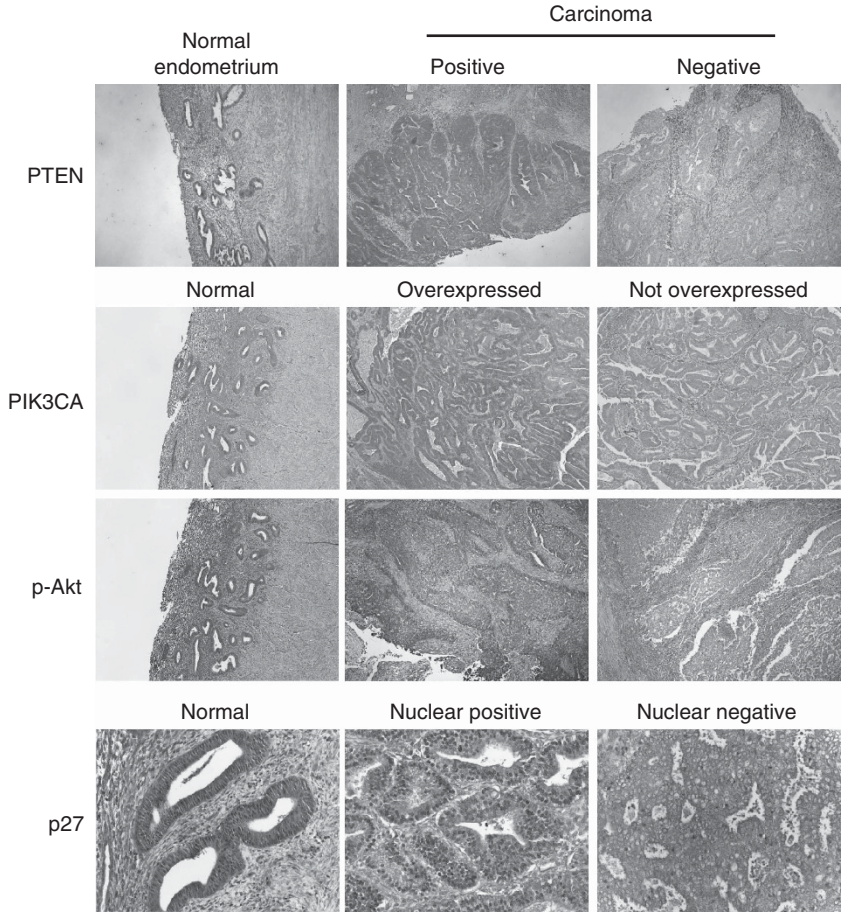

Figure 1. IHC staining patterns of PTEN, PIK3CA, p-Akt, and p27 in normal endometria and endometrial carcinomas. PTEN, PIK3CA, and p-Akt, × 100; p27, × 400.

Table 2. Results of IHC evaluation and correlation with p-Akt expression

		p-Akt overexpression		
Expression	**Number, *n* = 221**	**(+), *n* = 189**	**(−), *n* = 32**	***P*-value**
Negative PTEN (IHS = 0)	56 (25%)	51 (27%)	5 (16%)	0.19
Overexpressed PIK3CA (IHS > 6)	159 (72%)	148 (78%)	11 (34%)	1.6E − 06
Overexpressed p-Akt (IHS > 6)	189 (86%)	—	—	—
Negative nuclear p27 (0%)	143 (65%)	128 (68%)	15 (47%)	0.03

Abbreviations: IHC = immunohistochemical; IHS = IHC score; p-Akt = phosphorylated Akt.

Table 3. Relationship between IHC results and clinicopathological features

	PTEN expression			PIK3CA overexpression			p-Akt overexpression			Nuclear p27 expression		
Clinicopathological variables	**Negative $n=56$**	**Positive $n=165$**	***P***	**(+) $n=159$**	**(−) $n=62$**	***P***	**(+) $n=189$**	**(−) $n=32$**	***P***	**Negative $n=143$**	**Positive $n=78$**	***P***
Age ⩾70	5 (9%)	31 (19%)	0.10	26 (16%)	10 (16%)	1	31 (16%)	5 (16%)	1	25 (17%)	11 (14%)	0.57
Pre-menopause	19 (34%)	44 (27%)	0.31	43 (27%)	20 (32%)	0.51	49 (26%)	14 (44%)	0.055	44 (31%)	19 (24%)	0.35
Null parity	11 (20%)	26 (16%)	0.54	25 (16%)	12 (19%)	0.55	33 (17%)	4 (13%)	0.61	29 (20%)	8 (10%)	0.061
BMI > 30	11 (20%)	19 (12%)	0.17	20 (13%)	10 (16%)	0.26	24 (13%)	6 (19%)	0.40	21 (15%)	9 (12%)	0.68
DM	8 (14%)	31 (48%)	0.55	25 (16%)	14 (23%)	0.24	32 (17%)	7 (22%)	0.46	25 (17%)	14 (18%)	1
Endometrioid (*vs* Non-endometrioid)	53 (98%)	143 (88%)	0.03	139 (87%)	57 (92%)	0.48	171 (90%)	25 (78%)	0.064	133 (93%)	63 (81%)	0.008
G_1	30 (54%)	86 (52%)	0.88	84 (53%)	32 (52%)	0.88	102 (54%)	14 (44%)	0.34	84 (59%)	32 (41%)	0.016
MI > 1/2	17 (30%)	64 (39%)	0.34	55 (35%)	26 (42%)	0.35	68 (36%)	13 (41%)	0.69	56 (39%)	25 (32%)	0.31
LVI	14 (25%)	70 (42%)	0.025	58 (36%)	26 (42%)	0.54	71 (38%)	13 (41%)	0.84	58 (41%)	26 (33%)	0.31
FIGO stage III/IV	16 (29%)	51 (31%)	0.87	46 (29%)	21 (34%)	0.52	57 (30%)	10 (31%)	1	42 (29%)	25 (32%)	0.76

Abbreviations: BMI = body mass index; DM = diabetes mellitus; FIGO = International Federation of Gynecology and Obstetrics; IHC = immunohistochemical; LVI = lymphovascular invasion; MI = muscular invasion; p-Akt = phosphorylated Akt.

Next, we compared survival curves according to protein expressions (Figure 2). Patients with loss of PTEN expression showed significantly improved overall survival compared with those without PTEN expression loss (Figure 2A, $P=0.016$). In contrast, PIK3CA overexpression, p-Akt overexpression, and negative nuclear p27 did not show significant differences in overall survival (Figures 2B–D). When compared in subsets of stage I/II and III/IV, negative PTEN showed more favourable survival in advanced disease than in early disease (Figures 2E and F). Negative PTEN showed trends towards favourable survival, when compared in subsets of both pure endometrioid disease and disease other than pure endometrioid histology (Figures 2G and H).

We further conducted univariate and multivariate analyses of prognostic factors for overall survival. Among various prognostic factors, loss of PTEN expression, age ⩾70, G_1, FIGO stage III/IV, muscular invasion >1/2, and presence of LVI were found to be significant in the univariate analysis ($P=0.03$, <0.001, <0.001, <0.001, <0.001, and <0.001, respectively; Table 4). Among those significant factors, the following multivariate analysis demonstrated that loss of PTEN expression, age ⩾70, G_1, FIGO stage III/IV, and presence of LVI remained to be significant and independent factors ($P=0.03$, 0.04, 0.01, <0.001, and 0.03, respectively; Table 4).

Finally, we performed *PTEN* mutational analysis using DNAs from 33 archival tumour specimens (Table 5). A total of 27 mutations were detected in 19 samples. Mutations in exon 5 (9) and frameshift and missense mutations (12 each) were most frequent. Loss of PTEN expression (IHS = 0) in immunohistochemistry showed no correlation with the presence of *PTEN* mutation (67% *vs* 52%, $P=0.49$; Table 6). Interestingly, however, loss of PTEN expression was found to be significantly associated with the presence of frameshift or non-sense mutations, which result in PTEN protein truncation (67% *vs* 24%, $P=0.03$; Table 6).

DISCUSSION

Inactivation of the *PTEN* gene is the most frequent genetic defect in endometrial carcinoma. The most commonly observed *PTEN* defect is inactivation of both alleles by large deletion and mutation in each allele. Our IHC analyses showed that loss of PTEN expression (IHS = 0) was associated with endometrioid histology and absent lymphovascular invasion (Table 3). This observation suggests that tumours with loss of PTEN expression may have more indolent biological behaviour compared with tumours without PTEN loss. Furthermore, our survival analyses demonstrated that loss of PTEN expression was a significant and independent prognostic predictor for favourable survival in endometrial carcinoma (Table 4), keeping in line with the previously published findings on mostly limited sample size where *PTEN* mutation is associated with favourable prognosis (Risinger *et al*, 1998; Minaguchi *et al*, 2001; Sun *et al*, 2001; Salvesen *et al*, 2004). Collectively, our above findings utilising larger sample size suggest that loss of PTEN expression may have prognostic impact on survival through more indolent biological tumour behaviour, further confirming the prognostic significance of PTEN aberration.

Given the tumour suppressor function of PTEN (Minaguchi *et al*, 1999), one would expect that PTEN inactivation would imply poor prognosis. Endometrial cancers develop through accumulation of multiple genetic and epigenetic aberrations. Some tumours acquire malignant characteristics through PTEN inactivation, while others do so through aberrations of other genes; those aberrations may lead to more aggressive phenotype due to more detrimental molecular events than PTEN inactivation does. Meanwhile, another possible explanation for the impact of PTEN inactivation on good prognosis may be tumour suppressive roles of Akt, the pivotal effector downstream of PTEN (Wyszomierski and Yu, 2005). Akt reportedly blocks cancer cell mortality and invasion through the transcription factor NFAT (Yoeli-Lerner *et al*, 2005) or downregulation of RHO activity (Liu *et al*, 2006). The inhibitory effect of Akt activation on cancer cell cycle has also been reported (Kodama *et al*, 2002). Another study has indicated that Akt activation can promote tumorigenesis, but suppresses tumour invasion (Hutchinson *et al*, 2004). In our study, however, neither p-Akt nor p27 did show any prognostic significance for survival, although both proteins showed the expression patterns that are consistent with the signalling pathway. Accordingly, the observed PTEN impact on survival is not likely to be attributed to functions of downstream effectors but rather *PTEN* genetic aberration itself,

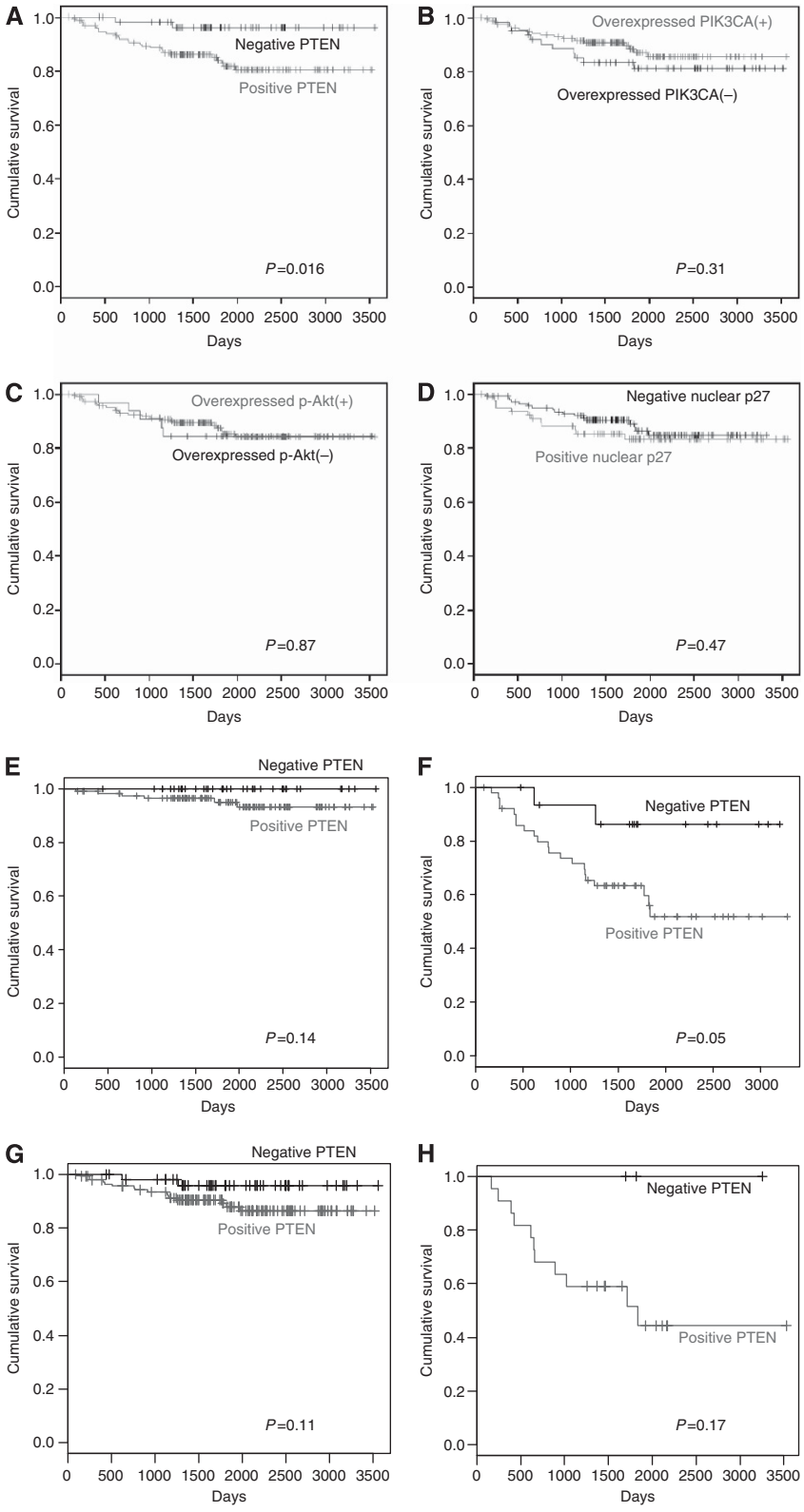

Figure 2. Kaplan–Meier curves for overall survival according to protein expression levels in endometrial carcinomas. (**A**) Patients with negative PTEN ($n=56$) *vs* positive PTEN ($n=165$); (**B**) patients with overexpressed PIK3CA ($n=159$) *vs* without overexpressed PIK3CA ($n=62$); (**C**) patients with overexpressed p-Akt ($n=189$) *vs* without overexpressed p-Akt ($n=32$); (**D**) patients with negative nuclear p27 ($n=143$) *vs* positive nuclear p27 ($n=78$); (**E**) patients with negative PTEN ($n=40$) *vs* positive PTEN ($n=114$) in early-stage disease (stages I and II); (**F**) patients with negative PTEN ($n=16$) *vs* positive PTEN ($n=51$) in advanced disease (stages III and IV); (**G**) patients with negative PTEN ($n=53$) *vs* positive PTEN ($n=143$) in pure endometrioid disease; (**H**) patients with negative PTEN ($n=3$) *vs* positive PTEN ($n=22$) in disease other than pure endometrioid histology.

Table 4. Univariate and multivariate analyses of prognostic factors for overall survival

	Univariate			Multivariate		
Prognostic factor	**HR**	**95% CI**	***P*-value**	**HR**	**95% CI**	***P*-value**
PTEN negative (*vs* positive)	0.20	0.05–0.86	0.03	0.21	0.05–0.88	0.03
PIK3CA overexpression (*vs* remainder)	0.68	0.32–1.43	0.31	—	—	—
p-Akt overexpression (*vs* remainder)	0.92	0.35–2.42	0.87	—	—	—
Nuclear p27 negative (*vs* positive)	0.76	0.37–1.60	0.47	—	—	—
Age⩾70 (*vs* <70)	3.67	1.69–7.98	<0.001	2.44	1.06–5.63	0.04
G_1 (*vs* G_{2-3}/non-endometrioid)	0.16	0.06–0.42	<0.001	0.28	0.11–0.76	0.01
FIGO stage III/IV (*vs* I/II)	10.9	4.44–26.9	<0.001	5.70	2.17–15.0	<0.001
MI>1/2 (*vs*⩽1/2)	9.50	3.62–24.9	<0.001	2.24	0.76–6.60	0.14
LVI present (*vs* absent)	7.42	3.02–18.2	<0.001	3.01	1.14–7.95	0.03

Abbreviations: CI = confidence interval; FIGO = International Federation of Gynecology and Obstetrics; HR = hazard ratio; LVI = lymphovascular invasion; MI = muscular invasion; p-Akt = phosphorylated Akt.

Table 5. PTEN mutational status and IHC score in endometrial carcinoma cases

Case	Histotype	Mutated exons	NCL	AA	NCL	AA	NCL	AA	NCL	AA	Mut	Mut only outside exons 5–7	PTEN truncation	IHS
1	G_2	8	963_964insA	T321fs*3							1	1	1	0
2	G_1	8	1008C>A	Y336*							1	1	1	0
3	G_2										0	0	0	4.5
4	Mixed										0	0	0	6
5	G_1										0	0	0	6
6	Mixed										0	0	0	0
7	G_2										0	0	0	6
8	G_1	5	389G>C	R130P							1	0	0	6
9	G_1	5	388C>G	R130G							1	0	0	6
10	G_1	8	907delA	I303fs*4							1	1	1	0
11	G_3	7	800delA	K267fs*9							1	0	1	6
12	Clear cell										0	0	0	6
13	G_1										0	0	0	0
14	G_2	5, 8	388C>G	R130G	962C>AT	T321fs*4					1	0	1	2
15	G_1										0	0	0	0
16	G_3	3, 5, 6, 6	208C>A	L70I	431A>C	K144Y	517C>T	R173C	601G>T	E201*	1	0	1	0
17	G_2	7	640_655>ACT	Q214fs*3							1	0	1	0
18	G_1	5	389G>A	R130Q							1	0	0	4
19	G_2	5, 9	405_406delAT	I135fs*44	1028TT>G	V343G					1	0	1	0
20	G_1	1	64_70del7bp	D22fs*2							1	1	1	0
21	G_1	7	710delA	K237fs*19							1	0	1	0
22	G_1	2	80G>A	Y27C							1	1	0	3
23	Mixed										0	0	0	3
24	G_2										0	0	0	3
25	Clear cell	1	38_39insC	K13fs*30							1	1	1	6
26	G_1	5, 6	440_441insA	K147fs*32	562_576>C	Y188fs*8					1	0	1	3
27	G_1	2	103A>G	M35V							1	1	0	6
28	G_1										0	0	0	9
29	G_1	5, 5	263A>G	Y88C	276C>G	D92E					1	0	0	9
30	G_2										0	0	0	0
31	G_2										0	0	0	9
32	G_1										0	0	0	3
33	G_1	6, 7	611delC	P204fs*17	796A>T	K266*					1	0	1	3

Abbreviations: AA = amino acid; IHC = immunohistochemical; IHS = IHC score; Mut = mutation; NCL = nucleotide.

Table 6. Relationship between PTEN mutational status and IHC results

PTEN IHC	Mutation in any exon	*P*-value	Mutation only outside exons 5–7	*P*-value	PTEN truncation	*P*-value
IHS = 0	8/12 (67%)	0.49	4/12 (33%)	0.38	8/12 (67%)	0.03
HIS > 0	11/21 (52%)		3/21 (14%)		5/21 (24%)	
IHS < 6	13/21 (62%)	0.72	5/21 (24%)	1.0	11/21 (52%)	0.07
HIS ⩾ 6	6/12 (50%)		2/12 (17%)		2/12 (17%)	

Abbreviations: IHC = immunohistochemical; IHS = IHC score.

which may represent the biological and clinical characteristics of tumour.

The antibody used for our PTEN immunohistochemistry, that is, 6H2.1, recognises the C-terminal 100 amino acids of PTEN protein. Theoretically, not all mutations of *PTEN* may be detected as altered protein expression. Frameshift and non-sense mutations that result in truncating the C-terminal 100 amino acids of PTEN should be observed as null staining, while missense mutations may not be recognised by altered staining. In fact, our mutational analysis demonstrated that loss of PTEN expression was not associated with *PTEN* mutational status, but rather with the presence of frameshift or non-sense mutations that produce truncated PTEN proteins (Table 6). It can be speculated that PTEN-truncating mutations may spare functionally important regions of PTEN protein, leading to better outcome, compared with tumours with other *PTEN* mutations and mutations of other genes. Indeed, we previously reported that *PTEN* mutation only outside exons 5–7 was an independent prognostic factor for favourable survival in endometrial carcinoma, possibly due to incomplete disruption of protein function by sparing functionally important elements located inside exons 5–7 (Minaguchi *et al*, 2001). However, the current study failed to find statistically significant correlation between loss of PTEN expression and mutations only outside exons 5–7 (Table 6). This discordance may be due to small sample size for mutational analysis in the current study. In any case, together with the published findings, our results further support the prognostic significance of *PTEN* aberration on favourable prognosis in endometrial carcinoma. Future studies are warranted to verify our observations as well as to elucidate mechanisms whereby PTEN inactivation affects tumour behaviour and patient prognosis.

Recently, various molecular agents targeting the PI3-kinase/PTEN/Akt pathway have been developed including mTOR inhibitors such as everolimus and temsirolimus, and numerous clinical studies are ongoing in endometrial cancer (Oza *et al*, 2011). Today, it is getting important in terms of health economics to identify biomarkers predicting the sensitivity of tumour to those expensive molecular agents. As our subset analysis showed a stronger trend of PTEN loss towards favourable survival in advanced-stage disease than in early-stage disease, patients with tumour negative for PTEN protein expression may benefit more from the therapeutics targeting molecules downstream of PTEN particularly in patients with advanced-stage diseases.

In conclusion, we have demonstrated here that loss of PTEN expression is a significant and independent predictor for favourable survival in endometrial carcinomas. The current data suggest that favourable outcome of tumours with PTEN expression loss may be due to more indolent biological behaviour of tumour. Furthermore, loss of PTEN expression was found to be associated with PTEN-truncating mutations. Our observations provide significant implications for the individualised management of endometrial cancer including the use of molecular targeted agents.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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