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Significance of progesterone receptor-A and -B expressions in endometrial adenocarcinoma

Tomoyuki Miyamoto[a,1], Jun Watanabe[a,b,2], Hiroki Hata[c,3], Toshiko Jobo[a,d,4], Miwa Kawaguchi[a], Manabu Hattori[e,5], Mayumi Saito[a], Hiroyuki Kuramoto[a,d,e,*]

[a] *Department of Clinical Cytology, Graduate School of Medical Sciences, Kitasato University, 1-15-1 Kitasato, Sagamihara 228-8555, Japan*
[b] *Department of Pathology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Sagamihara 228-8555, Japan*
[c] *Department of Obstetrics and Gynecology, Tokyo Posts and Telecommunications Hospital, 2-14-23 Fujimi, Chiyoda-ku 102-8798, Japan*
[d] *Department of Obstetrics and Gynecology, School of Medicine, Kitasato University, 1-15-1 Kitasato, Sagamihara 228-8555, Japan*
[e] *Department of Clinical Cytology, School of Allied Health Sciences, Kitasato University, 1-15-1 Kitasato, Sagamihara 228-8555, Japan*

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Abstract

The progesterone receptor (PR) has two isoforms, A and B, among which PR-B is mainly involved in regulating proliferation of the uterine endometrium. In this study, immunohistochemical analysis was carried out to investigate the correlation of PR-A and -B expressions with cell cycle-regulatory proteins and clinicopathological parameters in endometrial adenocarcinoma. One hundred and forty-one endometrioid adenocarcinomas [76 with well-differentiated (G1), 35 with moderately differentiated (G2) and 30 with poorly differentiated (G3)] were used. Specimens of formalin-fixed and paraffin-embedded tissue were immunohistochemically stained using the high polymer method (HISTOFINE, NICHIREI). The percentage of positive nuclei of tumor cells observed in three high power fields was expressed as a labeling index (LI). PR-B expression significantly occurred more frequently in G1. It was inversely correlated with p53 gene mutation and p53 over expression, and also with clinicopathological variables, including myometrial and lymph-vascular space invasion and the FIGO stage. Patients with negative PR-B had a poorer prognosis than positive cases. PR-A expression was also significantly higher in G1 and was inversely correlated with Ki-67 expression and myometrial invasion, but not with prognosis. PR-A and -B expressions were significantly correlated with biologically malignant potential. Especially, PR-B expression is useful as a prognostic indicator of endometrial adenocarcinoma.

Keywords: Progesterone receptor isoforms; Clinicopathological parameters; Endometrial adenocarcinoma; Prognosis

1. Introduction

Sex steroids such as estrogen, progesterone and androgen exert a variety of effects on target tissues in humans. In general, these biological effects are initially mediated through interactions with their native receptors. Estrogen stimulates cellular proliferation regulated by the estrogen receptor (ER), whereas progesterone inhibits cellular growth and induces differentiation regulated by the progesterone receptor (PR). Transcription of the PR gene is enhanced and maintained by estrogen [1].

The PR has two isoforms, A and B [2]. PR-B is composed of 933 amino acids, whereas PR-A lacks 164 amino acids from the N-terminus of PR-B. The two isoforms are transcribed from two promoters located in the PR gene. The role and function of each receptor isoform remains unclear, although PR-B may be mainly involved in regulating endometrial function. However, PR-B is necessary for activating progesterone target genes, whereas PR-A functions as a repressor of PR-B activity [3].

* Corresponding author. Tel.: +81 42 778 9276; fax: +81 42 778 9276.
E-mail address: kuramoto@cc.ahs.kitasato-u.ac.jp (H. Kuramoto).
[1] Tel.: +81 42 778 9276; fax: +81 42 778 9276.
[2] Tel.: +81 42 778 9020; fax: +81 42 778 8441.
[3] Tel.: +81 35 214 7013.
[4] Tel.: +81 42 778 8414; fax: +81 42 778 9433.
[5] Tel.: +81 42 778 9633; fax: +81 42 778 9648.

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Endometrial adenocarcinoma is the most common form of gynecologic malignancy [4]. Traditional factors associated with its prognosis include tumor grade, depth of uterine myometrial invasion and stage [5]. We previously showed that cell cycle-regulatory proteins such as Ki-67, cyclin E, cyclin A, cyclin D1, cyclin-dependent kinase (cdk) 2, p27 and p53 were correlated with the malignant potential of endometrial adenocarcinoma [6–11]. In addition, the most extensively studied biologic markers in endometrial carcinoma are ER and PR. High levels of ER and PR are directly correlated with a lower tumor grade, less myometrial invasion and a lower incidence of lymph node metastases. In addition, they can be independently used to predict a patient's survival prognosis [4].

The expressions of PR-A and -B isoforms in endometrial adenocarcinoma and their involvement in its pathogenesis are not known. Therefore, immunohistochemical analysis was carried out in this study to investigate the significance of PR-A and -B expressions in endometrial adenocarcinoma, including in the normal endometrium and endometrial hyperplasia. The correlations of PR-A and -B expressions with cell cycle-regulatory proteins such as Ki-67, cyclin E, cyclin A, cyclin D1, cdk2, p27 and p53, clinicopathological parameters and prognosis of endometrial adenocarcinoma were also analyzed.

2. Materials and methods

2.1. Materials

Tissue samples of 141 endometrioid type endometrial adenocarcinomas [76 with well-differentiated (G1), 35 with moderately differentiated (G2), 30 with poorly differentiated (G3) adenocarcinomas], 16 normal endometria (6 with proliferative phase and 10 with secretory phase) and 17 endometrial hyperplasias [7 with simple hyperplasia (SH), 4 with complex hyperplasia (CH) and 6 with complex atypical hyperplasia (CAH)] were surgically obtained at Kitasato University Hospital with informed consent. No patients had received either adjuvant chemotherapy or radiotherapy before surgery. Surgical staging and histological diagnosis were assigned based on the criteria established by the International Federation of Gynecology and Obstetrics (FIGO) [12]. The mean age of these patients was 57 years (range of 35–83 years).

2.2. Immunohistochemical staining

Immunohistochemical staining for PR-A and -B was performed using the high polymer (HISTOFINE simple stain, NICHIREI) method. Tissue samples fixed in 10% formalin and embedded in paraffin were cut at 3 μm in thickness and mounted on slides. After dewaxing and rehydration, the sections were incubated in 3% hydrogen peroxide for 5 min at room temperature to quench endogeneous peroxidase activity. An autoclave unmasking process (15 min at 121 °C in 10 mmol/L citrate buffer, pH 6.0) was used. After allowing them to stand at room temperature for 30 min, the specimens were preincubated with 10% normal swine serum to reduce nonspecific reaction for another 30 min at room temperature. Then, they were incubated with mouse monoclonal anti-PR-A antibody (hPRa7, NEOMARKERS, 1:100 dilution) and anti-PR-B antibody (hPRa2, NEOMARKERS, 1:100 dilution) at 4 °C overnight. Following this, the specimens were rinsed twice with PBS for 5 min and incubated with HISTOFINE simple stain MAX-PO (multi) for 30 min. Peroxidase activity was visualized by treatment with 0.05% diaminobenzidine containing 0.6% hydrogen peroxide for 25 s. After the samples were rinsed in water, nuclei were counterstained with Mayer's hematoxylin. The sections were then dehydrated, cleared and mounted. Previously defined positive endometrial cancer tissues were used as positive controls.

These monoclonal antibodies were raised in a mouse against PR isoforms obtained from a human endometrial carcinoma (EnCa 101). Clarke et al. [13] reported that the hPRa7 antibody recognizes both PR-A and PR-B in immunoblot analysis. However, using immunohistochemistry, Mote et al. [14] reported that hPRa7 did not recognize PR-B in fixed tissues even after antigen retrieval, as evidenced by the absence of immunostaining by this antibody in the PR-B-expressing MDA-MB-231/PR-B cell line. This is believed to be due to the inaccessibility of the epitope on PR-B recognized by hPRa7 in 10% formalin-fixed and paraffin-embedded tissue specimens. In addition, Clarke et al. [13] reported that the hPRa2 antibody recognizes only PR-B in immunoblot analysis.

The results of PR-A and -B expressions were compared with those of Ki-67, cyclin E, cyclin A, cyclin D1, cdk2, p27 and p53, which had been analyzed at our laboratory [6–11]. In brief, for immunostaining of Ki-67, cyclin E, cyclin A, cyclin D1, cdk2, p27 and p53, rabbit polyclonal anti-Ki-67 antibody (DAKO, 1:50 dilution), mouse monoclonal anti-cyclin E antibody (13A3, Novocastra, 1:40 dilution), mouse monoclonal anti-cyclin A antibody (6E6, Novocastra, 1:100 dilution), mouse monoclonal anti-cyclin D1 antibody (DCS-6, Oncogene, 1:80 dilution), rabbit polyclonal anti-cdk2 antibody (M2, Santa Cruz Biotechnology, 1:2000 dilution), mouse monoclonal anti-p27 antibody (1B4, Novocastra, 1:200 dilution) and mouse monoclonal anti-p53 antibody (DO-7, Novocastra, 1:80 dilution) were used for a labeled streptavidin-biotin methods (LSAB kit, DAKO). Other procedures were same for PR-A and -B.

2.3. Evaluation of immunohistochemical staining

Distinct PR-A and -B nuclear staining was defined as positive. The percentage of positive nuclei in at least 1000 tumor cells seen under three high-power fields and counted at random was expressed as a labeling index (LI). Cases were defined as positive for immunostaining when the LI

was over 5.0%. The LI in each group was expressed as the mean ± standard deviation (S.D.).

2.4. Quantitative analysis of estrogen receptor (ER) and progesterone receptor (PR)

ER and PR levels in carcinoma tissues were measured using a radioreceptor assay or enzyme immunoassay at Kitasato Biochemicals Laboratory (Kanagawa, Japan). Tumors with over 20 fmol/mg protein were classified as ER or PR positive.

2.5. Comparison with clinicopathological variables

Clinicopathological parameters of the patients were introduced from the tumor registry of the Department of Gynecology, Kitasato University Hospital, and were compared with the results of PR-A and -B expressions.

2.6. Comparison with p53 gene mutation

Polymerase chain reaction-single strand conformation polymorphism (PCR-SSCP) analysis was performed to analyze p53 gene mutation as previously described by Hata et al. p53 gene analysis of endometrial carcinoma was randomly performed on 56 cases. In brief, the DNA of endometrial cancer tissue was extracted by a phenol–chloroform method. Oligonucleotide primer pairs in exons 5–8 of the p53 gene and PCR conditions conformed to the method of Uchida et al. [15]. Each 5′-end of the primer was labeled with [γ-^{32}P] ATP, and SSCP conformed using the method of Orita et al. [16]. Electrophoresis was performed at 40 W for 3 h on 5% polyacrylamide gel. The gel was dried at 80 °C for 45 min and exposed to Kodak XAR film at room temperature for 15 min to 24 h with an intensifying screen. DNA extracted from the lymphocytes of a woman with normal menstrual cycles was used as a normal control. Aberrant bands or mobility shifts indicated a positive gene mutation.

2.7. Statistical analysis

Statistical analysis of the correlation between the expressions of PR-A, -B and cell cycle-regulatory proteins of the same patients was conducted by the Spearman's rank correlation test. The Mann–Whitney *U*-test was used to examine the correlation of PR-A and -B LIs with clinicopathological parameters. The Kaplan–Meier method was used to examine the correlation of PR-A and -B expressions with patients' prognosis. A p value of less than 0.05 was considered to be statistically significant.

3. Results

3.1. PR-A and -B expressions in endometrial adenocarcinoma and comparison with normal endometrium and endometrial hyperplasia

Staining for PR-A and -B was positive in the nuclei of the cancer cells (Fig. 1).

The PR-A LI was 62.9 ± 36.7% in the proliferative phase of normal endometrium and 14.9 ± 31.5% in the secretory phase. PR-A expression in the former was significantly higher than that in the latter ($p = 0.0121$). In endometrial hyperplasias, the PR-A LIs were 77.6 ± 8.7% for SH, 51.3 ± 34.7% for CH and 63.7 ± 24.7% for CAH, and showed no statistical difference between hyperplasias. The LIs of PR-A in G1, G2 and G3 endometrial carcinomas were 13.7 ± 24.7%, 13.8 ± 27.7% and 2.4 ± 12.9%, respectively. PR-A expression in endometrial carcinomas was significantly lower for the higher histological grade (G1 versus G3: $p = 0.0079$). The LIs of PR-A in normal endometrium and endometrial hyperplasias were significantly higher than that for all endometrial adenocarcinomas, respectively ($p = 0.0153$ and <0.0001) (Table 1). The LIs of PR-A in the proliferative phase endometrium and each hyperplasia were significantly higher than that for G1 adenocarcinoma ($p < 0.0001$, <0.0001, 0.0137, and 0.0001) (Table 1).

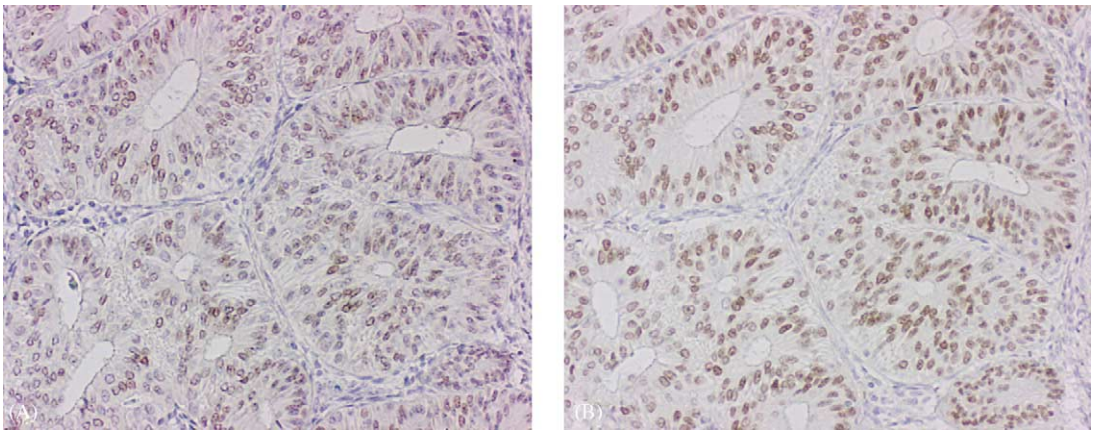

Fig. 1. Immunohistochemical staining for PR-A and -B in endometrial adenocarcinoma. Staining for PR-A (A) and PR-B (B) was positive in the nuclei of cancer cells of G1 adenocarcinoma (magnification 200×).

Table 1
PR-A expression in normal endometrium, endometrial hyperplasia and endometrioid adenocarcinoma

	No. of cases	PR-A LI (mean±SD)	p-value
normal endometrium	16	34.4±38.9	
prolifelative phase	6	62.9±36.7	*
secretory phase	10	14.9±31.5	
endometrial hyperplasia	17	66.5±23.5	
SH	7	77.6± 8.7	
CH	4	51.3±34.7	
CAH	6	63.7±24.7	
endometrioid adenocarcinoma	141	11.3±23.9	
G1	76	13.7±24.7	
G2	35	13.8±27.7	
G3	30	2.4±12.9	

*p<0.05: significant (Mann-Whitney U-test)
**p<0.01: significant (Mann-Whitney U-test)
†p<0.0001: significant (Mann-Whitney U-test)
SH: simple hyperplasia
CH: complex hyperplasia
CAH: complex atypical hyperplasia

The PR-B LIs were 68.0 ± 37.6% for the proliferative phase of the normal endometrium and 26.9 ± 42.4% for the secretory phase. The PR-B LI for the secretory phase tended to be lower, but there was no statistically significant difference. For endometrial hyperplasia, the PR-B LIs were 84.2 ± 6.0% for SH, 55.0 ± 36.9% for CH and 67.1 ± 8.0% for CAH, showing no statistical difference between hyperplasias. The LIs of PR-B for G1, G2 and G3 endometrial carcinomas were 38.8 ± 33.7%, 29.6 ± 35.8% and 9.7 ± 18.6%. PR-B expression in endometrial carcinomas was significantly lower for the higher histological grade (G1 versus G3: $p < 0.0001$). The LIs of PR-B for the normal endometrium and endometrial hyperplasias were significantly higher than that in all endometrial adenocarcinomas, respectively ($p = 0.0025$ and <0.0001) (Table 2). The LIs of PR-B in the proliferative phase endometrium and hyperplasias were significantly higher than that in G1 adenocarcinoma ($p = 0.003$ and 0.0002) (Table 2).

Table 2
PR-B expression in normal endometrium, endometrial hyperplasia and endometrioid adenocarcinoma

	No. of cases	PR-B LI (mean±SD)	p-value
normal endometrium	16	49.6±42.8	
prolifelative phase	6	68.0±37.6	
secretory phase	10	26.9±42.4	
endometrial hyperplasia	17	71.3±20.9	
SH	7	84.2± 6.0	
CH	4	55.0±36.9	
CAH	6	67.1± 8.0	
endometrioid adenocarcinoma	141	30.4±33.5	
G1	76	38.8±33.7	
G2	35	29.6±35.8	
G3	30	9.7±18.6	

*p<0.05: significant (Mann-Whitney U-test)
**p<0.01: significant (Mann-Whitney U-test)
†p<0.0001: significant (Mann-Whitney U-test)
SH: simple hyperplasia
CH: complex hyperplasia
CAH: complex atypical hyperplasia

Table 3
Correlation of PR-A expression in endometrial adenocarcinoma with cell cycle-regulatory protein expression

	p value	*r*'s
Ki-67	0.0253*	−0.193
Cyclin E	0.0305*	−0.194
Cyclin A	0.3165	−0.090
Cyclin Dl	0.8007	−0.021
cdk2	0.7860	−0.025
p27	0.0076*	−0.240
p53	0.2827	−0.092

Labeling indices of the expressions were compared.
* $p < 0.05$: significant (Spearman 1 rank correlation test).

3.2. Correlation of PR-A and -B expressions with cell cycle-regulatory proteins

The PR-A LI for endometrial adenocarcinoma was inversely correlated with the LIs of Ki-67 ($p = 0.0253$), p27 ($p = 0.0076$) and cyclin E ($p = 0.0305$), but not with those of p53, cdk2, cyclin A and cyclin D1 (Table 3).

The PR-B LI was inversely correlated with the LIs of p53 ($p = 0.0120$) and cyclin D1 ($p = 0.0109$), but not with those of Ki-67, p27, cdk2, cyclin A and cyclin E (Table 4).

3.3. Correlation of PR-A and -B expressions with clinicopathological parameters

PR-A expression was inversely correlated with myometrial invasion ($p = 0.0393$), whereas it was not correlated with the FIGO stage, lymph node metastasis, lymph-vascular space involvement (LVSI), group, biochemical ER and PR levels, menopause, p53 gene mutation (Table 5) or prognosis.

PR-B expression was significantly lower in FIGO stages IIIc and IV ($p = 0.0033$), and was inversely correlated with lymph node metastasis ($p = 0.0197$), LVSI ($p = 0.0364$) and myometrial invasion ($p = 0.0007$), but not with group or menopause. Immunohistochemical PR-B expression was positively correlated with biochemical ER ($p = 0.0281$) and PR ($p = 0.0398$) levels. In addition, PR-B LI was signifi-

Table 4
Correlation of PR-B expression in endometrial adenocarcinoma with cell cycle-regulatory protein expression

	p value	*r*'s
Ki-67	0.1847	−0.114
Cyclin E	0.2570	−0.102
Cyclin A	0.0723	−0.161
Cyclin Dl	0.0095*	−0.220
cdk2	0.6499	−0.041
p27	0.3464	−0.085
p53	0.0120*	−0.216

Labeling indices of the expressions were compared.
* $p < 0.05$: significant (Spearman 1 rank correlation test).

Table 5
Correlation of PR-A and -B expressions in endometrial adenocarcinoma with clinicopathological parameters

Clinicopathological parameters	No. of cases	PR-A LI (mean ± S.D.)	*p* value	PR-B LI (mean ± S.D)	*p* value
Stage					
FIGO I	89	11.6 ± 24.7		34.7 ± 34.1]	
FIGO II	18	13.2 ± 26.0		24.5 ± 33.1	
FIGO IIIa	16	13.4 ± 23.2	N.S.	36.5 ± 34.6	]0.0033*
FIGO IIIc	11	8.6 ± 21.8		12.4 ± 21.5]	
FIGO IV	4	0.0 ± 0.0		0.0 ± 0.0	
Lymph node metastasis					
Negative	103	12.8 ± 25.3	N.S.	34.1 ± 34.1	0.0197*
Positive	18	8.9 ± 22.3		16.3 ± 28.7	
Lymph-vascular space involvement (LVSI)					
Negative	91	13.4 ± 26.0	N.S.	35.2 ± 34.1	0.0364*
Positive	36	8.3 ± 20.0		22.9 ± 32.5	
Myometrial invasion					
<l/3	67	16.5 ± 27.5	0.0393*	40.0 ± 34.2	0.0007*
≧1/3	62	7.64 ± 20.3		22.7 ± 31.5	
Group					
1	63	13.0 ± 25.4		32.5 ± 33.7	
2	53	11.7 ± 25.0	N.S.	31.8 ± 33.9	N.S.
3	18	7.7 ± 17.9		25.8 ± 34.8	
ER (fmol/mg)					
<20	65	11.5 ± 24.5	N.S.	24.6 ± 33.6	0.0281*
≧20	33	13.4 ± 23.8		39.6 ± 30.3	
PR (fmol/mg)					
<20	51	8.3 ± 20.8	N.S.	22.6 ± 31.1	0.0398*
≧20	46	15.1 ± 26.3		36.4 ± 33.8	
Menopause					
Pre	41	17.7 ± 21.6	N.S.	33.1 ± 35.8	N.S.
Post	96	8.8 ± 28.3		29.8 ± 32.6	
p53 gene					
Wild	45	13.3 ± 24.1	N.S.	39.9 ± 32.3	0.0005*
Mutated	11	6.4 ± 21.3		0.7 ± 2.28	

N.S.: not significant. Group 1: coexisting with endometrial hyperplasia. Group 2: coexisting with normal endometrium. Group 3: entirely replaced by carcinoma.
* $p < 0.05$: significant (Mann–Whitney *U*-test).

cantly lower in cases with a p53 gene mutation ($p = 0.0005$) (Table 5).

Patients with negative PR-B had a poorer prognosis than those of positive cases ($p = 0.0046$) (Fig. 2).

4. Discussion

Our study showed that PR-A expression in normal endometrium was up-regulated in the proliferative phase and down-regulated in the secretory phase. In contrast, PR-B expression had a tendency to decline in the secretory phase, but it was not significant. In previous studies, total PR expression was also more frequent in the proliferative phase than the secretory phase, and two isoforms, PR-A and -B, were also more highly expressed in the proliferative phase [14,17–19]. PR-A has a regulatory and mitigating action on PR-B and other steroids, whereas PR-B is directly involved in regulating the endometrium [18,19]. We showed here that PR-A and -B expressions were higher in endometrial hyperplasia than in endometial adenocarcinoma. In contrast, Arnett-Mansfield et al. reported that only PR-A was expressed in 64% (7/11) of hyperplasia [20]. In our study, PR-A and -B were more frequently expressed in endometrial hyperplasia. This difference may be attributed to the sections that we used to diagnose hyperplasias, whereas they used hyperplastic lesions adjacent to adenocarcinoma. Endometrial hyperplasia is a precursor of endometrial carcinoma [21], and recent studies showed that genetic alterations in hyperplasias occurred at an increased frequency with dysplastic grade. Even the majority of complex hyperplasias (CH) have reportedly aberrant genetic profiles [22]. In our study, however, there was no significant difference between SH, CH and CAH in PR-A and -B expressions. Therefore, we postulate that there is no genetic alteration in PR-A and -B expressions among hyperplasias. Our results also suggest that in the proliferative phase endometrium and endometrial hyperplasia, PR status reflects excess

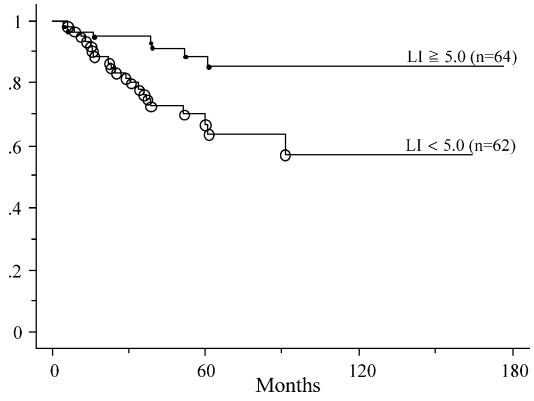

Fig. 2. Kaplan–Meier survival curves for PR-B positive (LI ≥ 5.0) and PR-B negative (LI < 5.0) patients. Patients with negative PR-B expression had a worse prognosis than for positive cases ($p = 0.0046$).

estrogenic action, by which the transcription of PR is enhanced [22,23].

We found that PR-A and -B expressions in endometrial carcinomas were significantly lower than those in hyperplasias, and were especially lower in G3 adenocarcinomas. PR expression was reported by several authors, including Kounelis et al. [5], who showed the occurrence of higher expression in low grade endometrial adenocarcinoma [4,24,25] and the existence of an inverse correlation between PR level and tumor grade [26,27]. In another study, endometrial carcinomas were found to express PR-A predominantly [20], although PR-A and -B expressions are inversely correlated with tumor grade. In our study, however, PR-B LI in endometrial carcinoma was more predominant than PR-A LI. Studies using cell lines also reported that PR-B was not expressed in poorly differentiated endometrial cancer cells [28,29]. From these data, we suggest that the lack of PR expression, including that of PR-A and -B, leads to a lack of progesterone protection against the growth-promoting effects of estrogen, and that the lack of PR expression is an early event in the carcinogenesis of endometrial adenocarcinoma. Wang-Rodriguez et al. also reported that PR expression was lower in Grade 3 breast carcinoma [30]. Furthermore, Inoue et al. showed that PR-A and -B were equally expressed in meningiomas, but that PR-B was predominant in astrocytic tumors and Schwannomas compared with PR-A [31]. Ishibashi et al. showed that in thymoma, PR-B was more frequently expressed than PR-A [1]. In the pancreas, Yeh et al. also found that PR was uniquely expressed in solid pseudopapillary tumors and stromal cells surrounded by mucinous cystic neoplasms [32]. These results suggest that PR isoform expressions may differ depending on tumors with an independent histological type.

Sasaki et al. has reported that hypermethylation of promoter-associated CpG islands was negatively associated with immunohistochemical staining for PR-B in endometrial adenocarcinoma [33]. Therefore, the loss of PR-A and -B expressions in G3 adenocarcinoma may be partly due to hypermethylation. We need further study to assess how often the loss of PR-A and -B expressions occur with relation to hypermethylation of promoter-associated CpG islands.

The LI of PR-A was inversely correlated with those of Ki-67, cyclin E and p27 as seen in our study, whereas the LI of PR-B was inversely correlated with those of cyclin D1 and p53. In our previous study, these cell cycle-regulatory proteins were found to be correlated with malignant potential [11]. In brief, the expressions of cyclin D1, cyclin E, p27 and p53 were positively associated with histological grade. The expression of cyclin E was significantly correlated with LVSI and myometrial invasion. p27 is correlated with the FIGO stage, LVSI and lymph node metastasis, and p53 is correlated with the FIGO stage, LVSI and myometrial invasion. The expressions of cyclin D1, cyclin E, p27 and p53 were positively correlated with Ki-67 expression. In the present study, PR-A and -B expressions were inversely correlated with higher histological grade and the loss of PR-A and -B expressions were also correlated with malignant potential. In addition, PR-B expression was more frequent in carcinomas with the wild type p53 gene. Rose showed that mutation of the p53 gene was associated with the absence of PR [4]. Also, Chou et al. reported that cyclin D1 expression was up-regulated in mammary epitherial cells in PR-A transgenic mice [34]. However, cyclin D1 expression was inversely correlated with PR-A in our study. These contradictory results may be because the PR found in the endometrium is different from that found in the mammary gland. PR-B expression showed an inverse tendency in Ki-67 expression in the present study, although this was not significant. A previous report showed that PR-B expression in the human thymoma is inversely correlated with Ki-67 expression [1].

We showed that PR-B was inversely correlated with clinicopathological prognostic factors, including myometrial invasion, LVSI and the FIGO stage. PR-A was also inversely correlated with myometrial invasion. Previous reports found that total PR expression in endometrial adenocarcinoma was associated with clinicopathological parameters, including prognosis [4,5,27,35]. Arnett-Mansfield et al. suggested that PR-A and -B expressions were inversely correlated with the FIGO stage [20]. Fukuda et al. reported that total PR immunohistochemistry was the most reliable means for predicting survival in endometrial adenocarcinoma, which was independent from other clinicopathological parameters, including stage, tumor grade, myometrial invasion and ER [27]. In our study, we first showed that negative PR-B expression (LI < 5.0) in patients with a poor prognosis was correlated with malignant potential. In breast carcinomas, Nakamura et al. observed that total PR expression was not associated with long-term survival (250 months) [36], whereas for neurogenic tumor and thymoma it was associated with growth, proliferation and prognosis [1,31]. Therefore, the significance of PR expression in patients' prognosis might be tumor specific. For endometrial adenocarcinoma, we suggest that PR-B immunohistochemistry is useful for predicting patients' prognosis.

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