

# Evaluation of Expression of the *PTEN* Gene, Oestrogen and Progesterone Receptors as Diagnostic and Predictive Factors in Endometrial Cancer

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**Abstract** Endometrial cancer belongs to the commonest malignancy in females after breast cancer, malignant neoplasm of female genitals in Europe and North America but there is still not significant improvement as far as the curability of this neoplasm is concerned, especially its advanced forms. That is why there is need to define new factors that could be not only diagnostic but also predictive factors. In present study we analyzed the mRNA *PTEN* expression by quantitative real-time polymerase chain reaction (Q-PCR) in 123 women of

endometrial carcinoma and 14 women of control group. Moreover we assessed oestrogen (ER) and progesterone receptors (PgR) in all cases. We defined the correlation between expression of *PTEN* gene and receptors and between *PTEN* expression and maturity grade of cancer. Neoplasm advancement grade G1 was diagnosed in 82.11 % of patients ( $n=101$ ), G2 in 9.76 % of patients ( $n=12$ ) and G3 in 8.13 % of patients ( $n=10$ ). Presence of ER and PgR and decreased expression of *PTEN* gene was found in majority of patients with endometrial cancer (79.12 % and 59.34 % respectively) and the most numerous group was with weak expression of ER and strong expression of PgR. There was no statistically significant difference in gene expression depending on receptors expression nor maturity grade of cancer ( $p>0.05$ ). Evaluation of expression of *PTEN* gene may turn out to be a very useful tool aimed at qualifying patients for different therapies of endometrial cancer and at searching of new diagnostic and therapeutic methods of this cancer independently on its receptor status nor maturity grade of cancer.

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## Introduction

Endometrial cancer (EC) is the most frequent, after breast cancer, malignant neoplasm of female genitals in Europe and North America and the fourth among all malignant neoplasms in women, after breast cancer, lung cancer and large intestine cancer [1–3]. EC cancerogenesis is not fully recognized process regarding many risk factors. Prognostic factors commonly used to identification of endometrial cancer present an incomplete picture of the tumour biology of endometrial cancer [4]. Therefore, investigation of other prognostic factors

is of special clinical relevance, particularly in view of the unexpectedly progressive course of the disease and frequent relapses in some cases. *PTEN* is the most frequently mutated gene identified yet in endometrial cancers [5, 6].

*PTEN* (Phosphatase and Tensin Homologue) is a suppressor gene located in chromosome 10q23. It codes lipid and protein phosphatase (PTEN) and contributes to the control of the proliferation, differentiation and apoptosis process [7]. The *PTEN* tumor suppressor gene regulates the oncogenic phosphatidylinositol 3-kinase (*PI3K*) signaling pathway that is involved in carcinogenesis. Downstream of those two pathways is *AKT*, a serine-threonine kinase that is regulated by *PI3K* and influences apoptosis and cell proliferation [7]. Alterations in the *PTEN-PI3K-AKT* pathways have been reported for hormone-related tumors among women, including breast, ovarian [8, 9] and endometrial [5, 6] cancers. Until now it has been found that *PTEN* mutations are the most frequent genetic changes in endometrial cancer of type I and occur in 25–83 % of tumours, including tumours with microsatellite instability [10]. *PTEN* inactivation was described most frequently in early stages of endometrial cancer whilst in other types of neoplasms it occurs in their more advanced stages and is connected with cancer cells metastases [11]. Due to this fact, *PTEN* may be a good endometrial cancer marker, already in the early stage of its development [12, 13].

*PTEN* expression correlates negatively with neoplasm advancement grade. *PTEN* mutations, occurring in an early development stage of the tumour, result in lack of cell differentiation, which might be connected with a more aggressive neoplasm type [14, 15].

In light of substantial evidence that the progression of endometrial cancer can be associated with *PTEN*, it seems reasonable to check a possible correlation between the expression of this gene and clinical status of endometrial cancer patients.

## Material and Methods

### Patients

Endometrium was obtained from 137 women who underwent hysterectomy with adnexectomy in the Gynaecological and Obstetric Clinical Hospital of the University of Medical Sciences in Poznan between 2004 and 2006. Tumour tissues were obtained from women with endometrial adenocarcinoma. Clinical data for the patients and histological data were registered. There were 123 women and their mean age was  $60,6 \pm 10,0$  years (range: 34–85 years). Endometrium from age-matched, cancer-free women ( $n=14$ ) served as control (the mean age  $60,1 \pm 7,6$ ). Endometrial carcinomas were classified according to the criteria of the International Federation of Gynecology and Obstetrics (FIGO). Histological typing and grading were done according to the WHO classification.

Before the surgery each patient underwent a subject examination, a gynaecological examination, an ultrasonographic examination by means of an intravaginal probe and preoperative laboratory tests. Moreover, a conscious written consent to operation and uptake of segments of the endometrium for the sake of scientific research was signed by every patient.

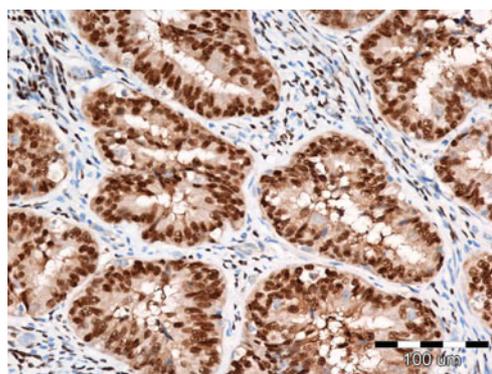
Tissue material obtained after the operation from each patient was divided into two parts. From one part wax blocks were created, and after that specimens for histopathological assessment dyed with hematoxylin and eosin (H + E). The other part of the material was frozen in  $-80$  °C. The procedures, used in the study, were approved by the Ethical Committee of the Medical University of Poznań (Poland).

### Evaluation of ER and PR

ER and PR status was determined by immunohistochemical method as part of the routine clinical practice. In this method ready antibodies Monoclonal Mouse Anti-Human Progesterone Receptor Clone PgR 636 and Monoclonal Mouse Anti-Human Oestrogen Receptor  $\alpha$  Clone ER 1D5 were used. Using the immunohistochemical assay, tumors were classified as positive if more than 10 % of the cells showed nuclear staining for the receptor. This information was received together with the characteristics of clinical material. Figure 1 shows the quality of immunohistochemical reactions.

### Quantitative Real-Time RT-PCR

Samples were stored at  $-80$  °C until RNA preparation. In the frozen specimens, after isolating RNA (ribonucleic acid) and rewriting it into cDNA (complementary deoxyribonucleic acid) in the reverse transcription reaction, the expression level of the *PTEN* gene was assessed by means of the real-time PCR (polymerase chain reaction) method. RNeasy Mini Kit by Qiagen, a QuantiTect Reverse Transcription kit by Qiagen, TaqMan Array 96-WellPlates Applied Biosystems with an appropriate set of primers for the examined gene were used.



**Fig. 1** ER expression in tumor tissue. IHC staining, original

18S rRNA (ribosomal ribonucleic acid) constituted the internal control of the reaction. The reaction was repeated three times for each specimen. On the basis of the Ct value (threshold cycle—the number of reaction cycles after which fluorescence exceeds the defined threshold) of the examined gene and of the internal control gene the relative expression level of RNA was calculated according to the  $\Delta\Delta\text{Ct}$  (delta, delta Ct) approximation method.

### Statistical Analysis

The occurrence of statistically significant differences between expression of *PTEN* gene depending on receptors expression and on neoplasm maturity grade was checked by means of Kruskal—Wallis test.

The tests were carried out after obtaining a consent from the Bioethical Commission of the Academy of Medical Sciences of Karol Marcinkowski in Poznań (Resolution number 240/04 from 05.02.2004).

The tests were carried out in the Patomorphological Laboratory of the Gynaecological and Obstetric Clinical Hospital of the University of Medical Sciences in Poznań and in the Faculty and Institute of Histology and Embryology of the Academy of Medical Sciences in Wrocław.

The statistical analysis was carried out in the Faculty and Institute of IT (informatics) and Statistics of the University of Medical Sciences in Poznań. For the sake of the analysis STATISTICA v. 8 was used, for multiple comparisons Kruskal—Wallis test was applied, U Mann—Whitney test was used to carry out the descriptive statistics for individual groups.

### Results

In the final results of the histopathological examination neoplasm advancement grade G1 was diagnosed in 82.11 % of patients with endometrial cancer ( $n=101$ ), G2 in 9.76 % of patients ( $n=12$ ) and G3 in 8.13 % of patients ( $n=10$ ).

In 29 patients with endometrial cancer, it was impossible to mark receptors in the examined material. Out of the remaining 94, in 7 patients the lack of ER was detected and in 2 patients the lack of PgR. Expression of *PTEN* gene was possible to evaluate in 118 patients with endometrial cancer. Wherefore the number of patients in whom receptors and gene were marked together was 91. Taking these results into account it was possible to divide patients with endometrial cancer into the following subgroups according to receptor expression intensification level. There were 17 patients in subgroup ER++/PgR+ (strong expression of ER and strong expression of PgR), 6 patients in subgroup ER++/PgR0 (strong expression of ER and weak or no expression of PgR), 44 patients in ER+/PgR+ (weak expression of ER and strong expression of

PgR), 17 patients in ER+/PgR0 (weak expression of ER and weak or no expression of PgR), 5 in ER0/PgR+ (no expression of ER and strong expression of PgR) and 2 patients in subgroup ER0/PgR0 (no expression of ER and weak or no expression of PgR). Dependencies of the presence of *PTEN* expression on the receptor status of patients with endometrial cancer are displayed in Table 1. In each receptor subgroup it was determined whether *PTEN* gene expression in the examined material was higher or lower than gene expression in the control group. Figure 2 shows summary of expression of *PTEN* gene depending on expression of ER and PgR.

By means of the Kruskal—Wallis test for multiple comparisons the occurrence of statistically significant differences between expression of *PTEN* gene in particular receptor subgroup was checked. No statistically significant difference in the field of the examined parameters was found.

Statistically significant differences between groups G1, G2 and G3 were examined in the event of  $\Delta\Delta\text{Ct}$  for gene *PTEN*. The assumed significance level was  $p < 0.05$  (Table 2).

No statistically significant difference in gene expression depending on neoplasm maturity grade was found.

### Discussion

In this paper, apart from expression of *PTEN* and ER and PgR receptors in endometrial cancer, the following issues were examined: the occurrence of dependencies between intensification of *PTEN* expression and expression of receptors as well as the occurrence of statistically significant differences in gene expression depending on malignancy grade G of endometrial cancer.

Loss of *PTEN* expression is connected, through trail PI3K/AKT, with loss of control of cell proliferation and apoptosis and with the promotion of neoplasm development [16]. Reduction of *PTEN* expression ensues most frequently through point mutations, loss of heterozygosity and promoter hypermethylation [17]. Somatic mutations of *PTEN* are common in endometrial cancer but occur mainly in type I cancer (in ca. 83 %) [10, 18–20]. Germinal mutations of *PTEN* occur in Crowden syndrome in 80 % of instances [21]. Loss of heterozygosity occur in 40 % of instances of endometrial cancer [22–25] and hypermethylation in circa 20 %, mainly in highly advanced cancers [26]. Matias-guiu et al. [23] report the occurrence of mutation and reduction of *PTEN* expression already during the hyperplasia stage. Similar data regarding *PTEN* inactivation, during the hyperplasia stage with or without atyp, occur in reports of Prat et al. [24] as well as Doll et al. [12]. Mutter et al. [11] found decreased expression in 75 % of instances of the pre-cancer stage and in 95 % of type I cancer and in 25 % of type II cancer, which let them draw the following conclusion: disorders in *PTEN* expression are an early incidents in the development process of endometrioid

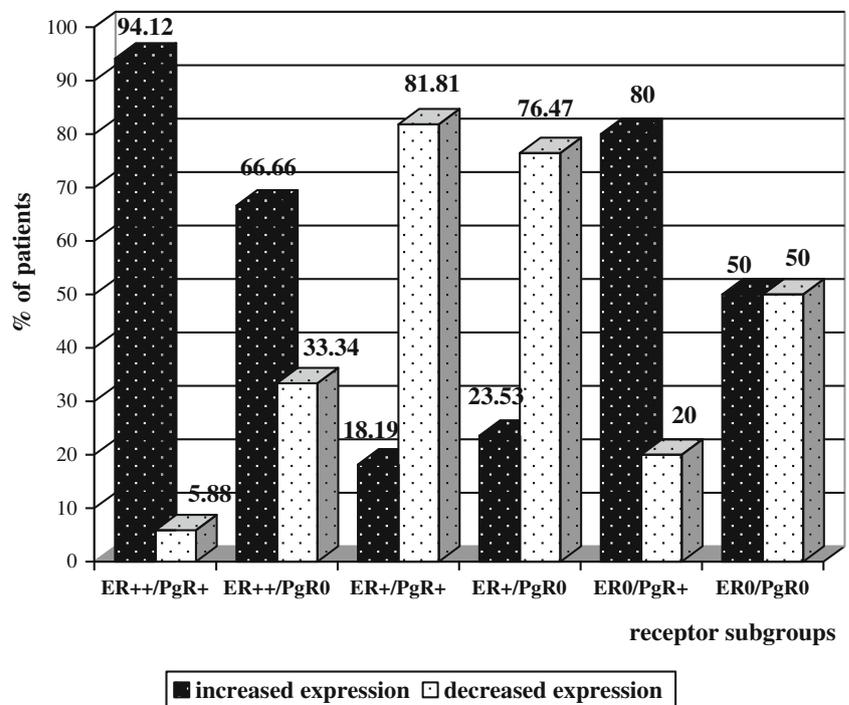
**Table 1** *PTEN* with altered expression in endometrial cancer patients ( $n=91$ )

<i>PTEN</i>	ER++/PgR+ ( $n=17$ ) Number (%)	ER++/PgR0 ( $n=6$ ) Number (%)	ER+/PgR+ ( $n=44$ ) Number (%)	ER+/PgR0 ( $n=17$ ) Number (%)	ER0/PgR+ ( $n=5$ ) Number (%)	ER0/PgR0 ( $n=2$ ) Number (%)
Increased expression	16 (94.12)	4 (66.66)	8 (18.19)	4 (23.53)	4 (80)	1 (50)
Decreased expression	1 (5.88)	2 (33.34)	36 (81.81)	13 (76.47)	1 (20)	1 (50)

endometrial cancer. Salvesen et al. [27] found the occurrence of promoter hypermethylation and decreased *PTEN* expression linked to this fact in 26 out of 138 patients (19 %) with endometrial cancer. Tests showed statistical significance regarding the occurrence of hypermethylation in advanced cancer stages. Latta et al. [28] found mutation of gene *PTEN* both in the normal endometrium exposed to oestrogens, pre-cancer stages as well as endometrial cancer. However, the percentage of patients with decreased expression of *PTEN* increased with the advancement of changes within the endometrium and amounted to 18–55 % for pre-cancer stages and 26–80 % for cancer. Salvesen et al. [29] in their further research reported the presence of mutations in 54 % of incidences of cancer and statistically significant dependency between the occurrence of mutations and young age of patients, low advancement according to FIGO, endometrioid cancer type, high maturity grade G, the occurrence of microsatellite instability as well as poor prognosis. Also Mackay et al. [30] noticed in their research on 123 patients beneficial prognosis in instances of decreased *PTEN* expression in women with an advanced endometrial cancer. However, Erkanli et al. [31], finding more significant reduction of expression in cancers than in

hyperplasia or normal endometrium, report the occurrence of statistically significant correlation between the reduction of expression and shorter survival time. Comparisons of expression degree of *PTEN* depending on neoplasm maturity were made by Inab et al. [32] as well as Kagan et al. [33]. They presented data which indicates a statistically significant dependency between maturity grade G and gene expression. Both testes showed more decreased expression in grade G1 and G2 than in G3. Moreover, Kagan found lower *PTEN* expression in specimens with positive expression of oestrogen and progesterone receptors. This difference was statistically significant. Sobczuk et al. [34] examining expression of this gene in 70 patients with cancer and 68 with normal endometrium found a significant difference in the reduction of *PTEN* expression between these two groups. Bogusiewicz et al. [35] examining among others *PTEN* expression in 45 women with primary endometrioid endometrial cancer found the reduction of *PTEN* level in 33 % of incidences and lack of correlation between the reduction of expression of this gene and the occurrence of endometrial cancer.

In this paper decreased expression of gene *PTEN* was found in 59.34 % of examined patients ( $n=54$ ), which

**Fig. 2** Relationship between *PTEN* and ER and PgR expression

**Table 2** Analysis of *PTEN* gene expression according to histological stage of endometrial cancer

Dependent: $\Delta\Delta\text{Ct } PTEN$	Value p for multiple comparisons (bilateral); $\Delta\Delta\text{Ct } PTEN$ Independent variable (grouping): maturity grade G Kruskal-Wallis: $H(2, N=118)=5.422665$ $p=.0664$		
	G 1	G 2	G 3
G 1		0.151903	0.855077
G 2	0.151903		0.076082
G 3	0.855077	0.076082	

confirms the thesis about the contribution of these gene to pathogenesis of endometrial cancer. However, a significant difference was noticed between the percentage of patients with overexpression and decreased expression of gene *PTEN* in individual receptor subgroups. Low expression was found in 76.47 % of patients from subgroup ER+/PgR0 and in 81.81 % of women from subgroup ER+/PgR+. In subgroups ER++/PgR+, ER++/PgR0 and ER0/PgR + the amount of *PTEN* mRNA was decreased in 5.88 %, 33.34 % and 20 % of incidences respectively, which in comparison with world reports is not without any meaning either. Subgroup ER0/PgR0, in which 50 % of patients had decreased expression, requires some explanations. However, due to the fact that this subgroup includes only 2 people, the results might not be reliable. Despite such a big percentage of patients with decreased expression of gene *PTEN* no statistically significant dependency regarding histological maturity grade has been found.

In research on the theory based on molecular rules of development of endometrial cancer attention has been drawn to a group of pharmaceuticals being mTOR inhibitors. mTOR (mammalian target of the rapamycin) is a protein (serine/threonine protein kinase) which constitutes a part of the trail regulating cell proliferation, growth and apoptosis (mTOR-AKT-PI3K-PTEN). In vitro tests showed sensitivity of endometrial cancer cells with *PTEN* inactivation to mTOR inhibitors. It happens because loss of *PTEN* leads to activation of many trails enhancing the activity of mTOR and at the same time uncontrolled cell growth [36]. Pharmaceuticals in this group include: temsirolimus (CCI-779), everolimus (RAD001) and deforolimus (AP23573) [10]. In tests carried out in 19 patients in an advanced endometrial cancer stage a partial response to treatment in 5 women (26 %) was found as well as inhibition of the development of the disease in 12 patients (63 %) [36, 37]. Other pharmaceuticals that are taken into account whenever *PTEN* expression is decreased include PI3K inhibitors (enzastaurin) and AKT inhibitors (tricitriline) [10]. Due to this fact it seems justified to evaluate expression of *PTEN* and to begin a therapy based on this evaluation in patients suffering from endometrial cancer, especially in advanced incidences where other methods become ineffective or impossible to carry out.

Tests regarding expression of *PTEN* gene presented in this paper are in most cases compliant with the results obtained by other scientists and indicate their significant usefulness in the process of search for new endometrial cancer therapeutic methods as well as create new possibilities regarding use of *PTEN* markers as a predictive factor. However, it is a novelty to compare gene expression in hormone-dependent and hormone-independent groups. This gives a possibility to work out a treatment method individualized for each patient by means of e.g. mTOR inhibitors, PI3K inhibitors and AKT inhibitors as well as hormonotherapy.

## Conclusions

1. Decreased expression of *PTEN* gene and expression of oestrogen and progesterone receptors occurs in the majority of patients with endometrial cancer.
2. Expression of *PTEN* gene and oestrogen and progesterone receptors is not dependent on each other.
3. Expression of *PTEN* gene is not dependent on the maturity grade of cancer.
4. Evaluation of expression of *PTEN* gene may turn out to be a very useful tool aimed at qualifying patients for different therapies of endometrial cancer and at searching of new diagnostic and therapeutic methods of this cancer, especially in relation with rare neoplasms and those with a poor prognosis, independently on their receptor status nor maturity grade of cancer.

**Conflict of Interest Statement** Authors declare that they have no conflict of interest.

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