Review paper

PTEN gene mutations in malignant tumours – a systematic review and clinical implications for tumour treatment

Mutacje genu PTEN w nowotworach złośliwych – przegląd systematyczny oraz implikacje kliniczne w leczeniu nowotworów

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Słowa kluczowe: kancerogeneza, mutacje genu PTEN, mutacje MMAC-1, mutacje TEP-1, genetyka onkologiczna.

Abstract

Introduction: The PTEN (phosphatase and tensin homologue deleted on chromosome 10) gene is one of the most commonly mutated suppressor genes in malignant tumours. PTEN protein counteracts the process of carcinogenesis by inhibition of many kinases promoting cell proliferation.
Aim of the research: A review and analysis of detected PTEN gene mutations in malignant tumours and identification of the most commonly mutated sites in the PTEN gene.
Material and methods: The systematic review included 70 publications.
Results: Mutations in the PTEN gene were found in 18% of cases. The largest number of mutations were observed in endometrial cancer – 49% of examined patients. Mutations most frequently occurred in exon 5 (49% of examined cases), followed by exon 8 (15% of cases) and exon 7 (13% of cases).
Conclusions: The identification of mutations in the PTEN gene in malignant tumours is of great clinical importance – targeted treatment with temsirolimus and everolimus is available for patients.

Streszczenie

Wprowadzenie: Gen PTEN (*phosphatase and tensin homolog deleted on chormosome 10*) jest jednym z najczęściej zmutowanych genów supresorowych w nowotworach złośliwych. Białko PTEN przeciwdziała procesowi kancerogenezy poprzez hamowanie wielu kinaz promujących proliferację komórek.
Cel pracy: Przegląd oraz analiza wykrytych mutacji genu PTEN w nowotworach złośliwych oraz wskazanie miejsc w genie PTEN, które najczęściej ulegają mutacji.
Materiał i metody: Do przeglądu systematycznego włączono 70 publikacji.
Wyniki: Mutacje genu PTEN stwierdzono w 18% przypadków. Najwięcej mutacji wykryto w przypadku raka endometrium – u 49% przebadanych pacjentów. Mutacje występowały najczęściej na eksonie 5 (49% przypadków), następnie na eksonie 8 (15% przypadków) oraz 7 (13% przypadków).
Wnioski: Identyfikacja mutacji w genie PTEN w nowotworach złośliwych ma duże znaczenie kliniczne – dostępna jest celowana terapia z użyciem temsirolimusu oraz ewerolimusu.

Introduction

In 1997, the *PTEN* (phosphatase and tensin homologue deleted on chromosome 10) gene was identified as a suppressor gene, the loss of which results in the formation of various types of cancer. *PTEN* is the most commonly mutated suppressor gene in malignant tumours, with a frequency of mutation close to that of another suppressor gene – *p53* [1]. The protein product of *PTEN* counteracts the process of carcinogenesis by inhibition of many kinases promoting cell proliferation. In addition, it regulates the basic cell processes,

such as growth, differentiation, migration, adhesion, and survival of cells [2]. Its anti-cancer properties are due to the function of the phosphoinositide-3 lipid kinase (PI3K)/mammalian target of rapamycin(mTOR)/Akt pathway inhibitor [3].

The PI3K/mTOR/Akt pathway (Figure 1) is responsible for the control of many processes taking place in the cell. The binding of growth factor to receptor tyrosine kinase triggers activation of PI3K – directly or by adaptor protein – insulin receptor substrate. Subsequently, an active PI3K protein phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2) to phosphatidylinositol-3,4,5-trisphosphate (PIP3). PIP3 is an important second messenger in carcinogenesis. It causes phosphorylation of Akt by phosphoinositide-dependent protein kinase 1 (PDK1). Phosphorylated Akt protein activates mTOR (mammalian target of rapamycin) – a serine/threonine kinase, which triggers cell proliferation, their survival, movement, and invasion [3–5]. PTEN is the main negative regulator of the PI3K pathway; it has the ability to dephosphorylate the lipid substrate PIP3 into inactive PIP2 [1, 6, 7]. Therefore, it reduces the amount of PIP3 by inhibiting signals leading to cell growth and survival, and thus inhibits the process of cancer development [1]. In addition, PTEN plays other roles preventing carcinogenesis: it maintains chromosome stability, and controls the process of DNA repair by positive regulation of repair protein RAD51 [3]. The PTEN is also responsible for cell cycle arrest at phase G1 by Rb protein, giving the cell time to repair DNA damage, and when DNA repair is not possible it induces apoptosis [2, 5, 8].

The protein encoded by *PTEN* consists of 403 amino acids of total mass 55 kDa (Figure 2). It occurs in the cytoplasm, cell membrane, and nucleus. The PTEN enzyme is characterized as a dual specificity phosphatase; it causes dephosphorylation of phosphorylated lipids and proteins [1, 6, 7, 9]. The PTEN protein consists of N-terminal domain – phosphatase domain (from amino acid 14 – 185), C2 domain (from amino acid 190 – 350), C-terminal tail (from amino acid 351 – 400), and the PDZ binding domain (from amino acid 401 – 403). The N-terminal domain plays the role of phosphatase; here is an active site of the enzyme, whereas the C2 domain is responsible for PTEN binding to lipids and localization of the cell membrane. The C-terminal tail plays the role of protein stabilization and is responsible for its migration in the cell. The PDZ binding domain is responsible for the interaction between the PTEN protein and other proteins [9, 10]. In order to obtain phosphatase function the PTEN protein forms homodimers. This suggests that the process of dimerization is indispensable for the normal functioning of protein, and therefore a disturbed dimerization process leads to carcinogenesis [3].

Even though cell membrane lipids are the main substrate for PTEN phosphatase, this enzyme is present mainly in the cytosol inside the cell and in the cell nucleus. Only a small fraction of it is dynamically

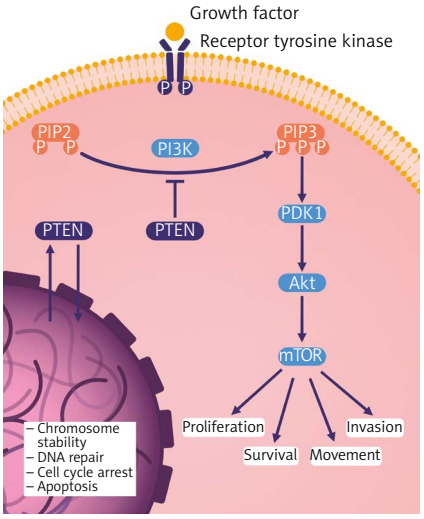

Figure 1. PI3K/mTOR/Akt kinase pathway with consideration of the role of PTEN

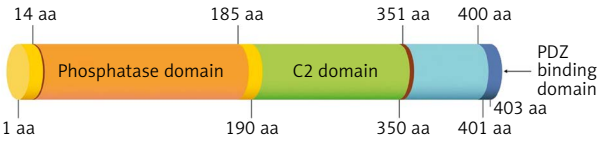

Figure 2. Structure of the PTEN protein (aa – amino acids)

related with the inner layer of the cell membrane. The PTEN interaction with the cell membrane is of critical importance. Mutations that do not concern the active site of the enzyme and cause impaired binding of the PTEN protein to the cell membrane, e.g. the deletion of the N-terminal fragment of the PIP2 binding protein, inactivate the PTEN protein by impairing its binding to the cell membrane, which prevents access of PTEN to its substrate [11]. It is thought that the function of the PTEN protein located in the nucleus differs from that of the protein located in the cytoplasm. The nuclear PTEN participates in the stabilization of chromosomes, DNA repair, and cell cycle arrest [12].

PTEN, also known as *MMAC1* (mutated in multiple advanced cancers-1), or *TEP1* (tensin-like phosphatase-1) is located on chromosome 10 at the 10q23.3 locus, and it contains 9 exons. In the promoter region in the gene, between -2233 and +1 pz, there are multiple CpG sequences and transcription factor binding sites: Egr-1, NF-κB, p53, RXR, and CREB. The *PTEN* promoter gene does not contain the consensus TATA sequence. Between -1190 and -1157 base pairs there are two p53 protein binding sites separated by 14 base pairs. The p53 binding sites are important in the *PTEN* promoter transactivation. Within intron 1 7 additional sequences have been observed similar to the p53 binding sites [6].

Exon 1 encodes the PIP2 binding site on codons 1–15, which naturally binds to the catalytic site to protect its binding site in the cell membrane. Exon

Figure 3. Scheme of the PTEN gene with consideration of exons and introns (1–9 – individual exons)

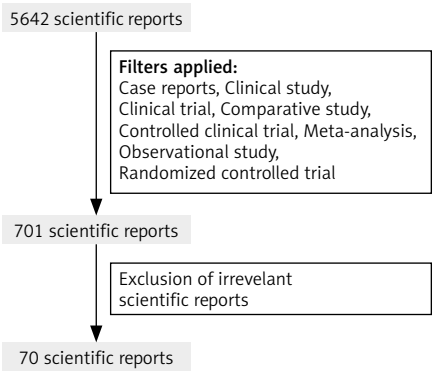

Figure 4. Algorithm of selection of reports

5 encodes the PTEN active site. Exon 7 encodes calcium binding region 3 (CBR3), which is of key importance for binding of the C-terminal fragment of the protein to the rest of the protein. It was confirmed that mutations within the CBR3 loop may completely disturb this binding. The combination of specified alternations in exons 1, 7, and 9 decreases the affinity of the PTEN to the cell membrane, thus exerting an effect on its activity [1] (Figure 3).

Disorders in *PTEN* expression due to genetic and epigenetic changes have been observed in many hereditary and sporadic cancers. Hereditary mutations of the *PTEN* in the germ cells cause Cowden syndrome [6]. This is an extremely rare disease characterized by the occurrence of multiple tumours of hamartoma type within the area of the skin, mucous membranes, gastrointestinal tract, breast, thyroid gland, and brain. In addition, this disease is associated with an increased risk of the development of, among others, breast cancer, thyroid cancer, and uterine cancer [13]. Somatic mutations of the *PTEN* and other proteins from the kinase mTOR – PI3K pathway were also found in pancreatic cancer, which is a significant clinical problem considering the delayed presentation of symptoms, aggressive course, and high mortality [14].

The lack, or considerable decrease in, the amount of PTEN in cancer cells may be associated not only with genetic changes, but also with epigenetic changes, mainly with an increased methylation of CpG dinucleotide sequences in the promoter region of the gene. Changes of this type were detected in endometrial cancer, prostate cancer, gastric cancer, colorectal cancer, non-small cell lung cancer, melanoma, and breast cancer [6].

Although *PTEN* is considered as a suppressor gene, inactivation of just one PTEN allele results in serious consequences for cell proliferation and survival. This phenomenon, called haploinsufficiency, is a condition in which only one normal allele in the diploid cell is insufficient to prevent disease caused by mutation in the other allele [15, 16]. It has been proven that haploinsufficiency of *PTEN* is responsible for the promotion of high-grade astrocytomas [17].

Aim of the research

The aim of the study was a review and analysis of the detected mutations of *PTEN* in malignant tumours in humans, and indication of the sites in *PTEN* that are most commonly mutated. The identification of these sites would allow the search for mutations in *PTEN*, and sequencing of the fragments of the gene the mutation of which causes malignant transformation.

Material and methods

Scientific reports were searched for in the PubMed database. The algorithm of the selection of reports is presented below (Figure 4). The following key words were introduced: *PTEN* AND mutation AND cancer, obtaining 5642 results. The following filters were applied: case reports, clinical study, clinical trial, comparative study, controlled clinical trial, meta-analysis, observational study, randomized controlled trial, obtaining 701 results. The reports were assessed for compliance with the subject of the presented study; ultimately, 70 scientific reports were included. The results were statistically analysed using Statistica software and presented in Tables 1 and 2 [18–83] and Figures 5–11.

Results

Almost all presented mutations are somatic mutations. If the mutation was germinal, it is indicated in the notes. More detailed tables containing codons and protein changes is presented in Supplementary Tables S1 and S2.

For the total number of cancers, the percentage of mutations is 0.1794 (18%), 95% C.I. is within the range 0.1674 (17%) – 0.1919 (19%) (Figure 5).

The largest number of mutations of *PTEN* was observed in the cases of endometrial cancer – mutation was found in 358 of 730 patients examined. Most often mutations were observed in exon 5, encoding the active centre of *PTEN* – 175 cases from the total of 330 (53%) (Figure 6). Mutations in exon 5 most often concerned codon 130 – 102 cases (31%). The second exon in which mutation was most commonly detected was exon 8 – 50 cases (15%), followed by exons 7, 6, and 1.

Considering glioma, the largest number of mutations was observed also in exon 5 – 13 cases per 39 (33%) (Figure 7). Mutations were most often found in codon 130.

In cases of breast cancer, it can be concluded that mutations most frequently concerned exon 5 – 35 cas-

Table 1. Results

No.	Author	Year	Number of cancers with detected PTEN mutation/number of patients examined (%)	Exon	Number of mutations in a given exon	Notes
			Pancreatic cancer			
1	Uemura *et al.* [18]	2018	1/1 (100%)	7	1	Germinal mutation
2	Young *et al.* [19]	2013	3/23 (13%)	Lack of data	Lack of data	–
			Breast cancer			
3	Kechagioglou *et al.* [1]	2014	19/43 (44.2%)	1	7	–
				5	34	–
				7	6	–
				9	6	–
4	Feilotter *et al.* [20]	1999	0/70 (0%)	–	–	–
5	Liang *et al.* [21]	2018	14/89 (15.7%)	Lack of data	Lack of data	–
6	Li *et al.* [22]	2018	15/313 (4.8%)	1	3	–
				3	1	–
				5	1	–
				6	2	–
				7	1	–
				8	5	–
				Intron 6	1	–
7	Stemke-Hale [23]	2008	2/88 (2.3%)	Lack of data	Lack of data	–
8	Mitus *et al.* [24]	2020	1/159 (0.62%)	3	1	Phyllodes tumour
9	Tang *et al.* [25]	2015	1/11 (9%)	Lack of data	Lack of data	
			Prostate cancer			
10	Kmak *et al.* [26]	2020	1/1 (100%)	8	1	–
11	Julka *et al.* [27]	2020	1/1 (100%)	Lack of data	Lack of data	Loss of exons 2–9
12	Wilkinson *et al.* [28]	2020	1/1 (100%)	Lack of data	Lack of data	–
13	Haffner *et al.* [29]	2013	1/1 (100%)	7	Lack of data	4–bp frameshifting deletion
14	Hussain *et al.* [30]	2018	34/87 (39%)	Lack of data	Lack of data	–
			Lung cancer			
15	Uruga *et al.* [31]	2020	2/2 (100%)	8	2	Lung adenocarcinoma Samples were subjected to genetic testing after the application of chemotherapy
16	Wang *et al.* [32]	2020	1/1 (100%)	7	1	Small cell lung cancer

Table 1. Cont.

17	Parikh *et al.* [33]	2018	1/1 (100%)	7	1	Small cell lung cancer
18	Hayashi *et al.* [34]	2018	1/1 (100%)	5	1	Small cell lung cancer
19	Miyoshi *et al.* [35]	2017	3/78 (4%) – large cell neuroendocrine carcinoma	Lack of data	Lack of data	–
			10/161 (6%) – small cell lung cancer			
			Mediastinal germ cell tumour			
20	Akizuki *et al.* [36]	2020	1/1 (100%)	5	1	–
			Ovarian cancer			
21	Matsubayashi *et al.* [37]	2019	1/1 (100%)	intron	–	c.1026+1G>T Germinal mutation Endometrial cancer of the ovary DNA of the tumour did not show mutation of the PTEN gene
22	Li *et al.* [38]	2019	3/62 (4.8%)	5	2	–
				6	1	
23	Yauy *et al.* [39]	2019	1/1 (100%)	5	1	Germinal mutation
24	McConechy *et al.* [40]	2014	5/30 (16.6%)	5	5	Endometrial cancer of the ovary
				6	1	
				8	4	
25	Fu *et al.* [41]	2012	1/21 (4.8%)	Lack of data	Lack of data	–
26	Kuo *et al.* [42]	2009	5/97 (5%)	Lack of data	Lack of data	–
27	Elvin *et al.* [43]	2017	2/125 (1.6%)	6	1	Clear cell carcinoma of the ovary
				7	1	
			Cervical cancer			
28	Wang *et al.* [44]	2018	5/32 (16%)	Lack of data	Lack of data	–
			Cholangiocarcinoma			
29	Sui *et al.* [45]	2019	1/2 (50%)	Lack of data	Lack of data	–
			Hepatocellular carcinoma			
30	Villanueva *et al.* [46]	2008	1/102 (1%)	Lack of data	Lack of data	–
			Endometrial cancer			
31	Kuno *et al.* [47]	2019	1/1 (100%)	8	1	–
32	Martignetti *et al.* [48]	2018	1/1 (100%)	5	1	–
				8	1	
33	Matsuura *et al.* [49]	2018	10/20 (50%)	5	5	–
				6	3	
				7	2	
				8	1	

Table 1. Cont.

34	McConechy *et al.* [40]	2014	185/276 (67%)	1	30	–
				2	5	
				3	1	
				5	150	
				6	23	
				7	20	
				8	44	
				9	3	
35	Oza *et al.* [50]	2011	17/33 (51.5%)	Lack of data	Lack of data	–
36	Wang *et al.* [44]	2018	10/17 (59%)	Lack of data	Lack of data	–
37	Kafshdooz *et al.* [51]	2015	0/75 (0%)	–	–	–
38	Djordjevic *et al.* [52]	2012	66/154 (42.9%)	Lack of data	Lack of data	The largest number of mutations in exon 8 (22.9% of mutations)
39	Polymeros *et al.* [53]	2020	25/57 (44%)	1	1	–
				2	1	
				5	9	
				6	2	
				7	4	
				8	3	
40	Kogan *et al.* [54]	2018	17/40 (42.5%)	5	9	–
				6	3	
				7	3	
				8	2	
41	Bendell *et al.* [55]	2018	1/12 (8.3%)	6	1	–
42	Obata *et al.* [56]	2016	1/1 (100%)	8	1	–
43	Ariura *et al.* [57]	2017	1/1 (100%)	5	1	–
44	Sullivan *et al.* [58]	2021	23/42 (55%)	Lack of data	Lack of data	–
			Uterine carcinosarcoma			
45	Hembree *et al.* [59]	2016	2/9 (22%)	5	1	–
				7	1	
			Melanoma			
46	Motaparthi *et al.* [60]	2019	1/1 (100%)	2	1	–
47	Zhou *et al.* [61]	2000	0/34 (0%)	–	–	–
48	Agosto-Arroyo *et al.* [62]	2017	1/1 (100%)	5	1	–

Table 1. Cont.

			Lymphoma			
49	Galanina *et al.* [63]	2019	1/1 (100%)	Lack of data	Lack of data	Peripheral T cell lymphoma
50	Ishiguro *et al.* [64]	2020	1/1 (100%)	7	1	Splenic marginal zone lymphoma
			T-cell acute lymphoblastic leukaemia			
51	Trinquand *et al.* [65]	2013	17/175 (10%)	Lack of data	Lack of data	–
			Follicular dendritic cell sarcoma			
52	Starr *et al.* [66]	2015	1/1 (100%)	7	1	Location of the tumour: thyroid gland
			Colorectal cancer			
53	Lin *et al.* [67]	2015	5/198 (2.5%)	1	1	–
				5	1	
				8	1	
54	Peeters *et al.* [68]	2013	15/288 (6%)	Lack of data	Lack of data	–
55	Li *et al.* [12]	2009	1/57 (1.75%)	8	1	Lack of PTEN expression in I HC: 95/327 (29%)
			Gastric cancer			
56	Byun *et al.* [69]	2003	0/55 (0%)	–	–	–
57	Werner *et al.* [70]	2013	5/16 (31%)	2	1	Gastric cancer and esophagogastric junction cancer
				9	1	
			Pancreatic neuroendocrine tumour			
58	Martin *et al.* [71]	2019	1/1 (100%)	1	1	–
			Hepatic angiosarcoma			
59	Tate *et al.* [72]	2007	1/ 2 (50%)	7	1	–
			Adenoid cystic carcinoma of salivary glands			
60	Falbo *et al.* [73]	2011	0/3 (0%)	–	–	–
			Glioma			
61	Staal *et al.* [74]	2002	1/1 (100%)	7	1	Germinal mutation
62	Kraus *et al.* [75]	2000	6/42 (14.3%)	Lack of data	Lack of data	Glioblastoma
63	Malmer *et al.* [76]	2001	0/8 (0%)	–	–	–
64	Reis *et al.* [77]	2001	2/2 (100%)	5	1	Glioblastoma – 2 tumours in 1 patient
				7	1	
65	Ohgaki *et al.* [78]	2004	78/332 (23.5%)	Lack of data	Lack of data	Glioblastoma

Table 1. Cont.

66	Actor *et al.* [79]	2002	9/20 (45%)	1	1	Gliosarcoma
				3	1	
				4	1	
				5	5	
				6	1	
				8	1	
67	Rasheed *et al.* [80]	1997	16/98 (16.3%)	1	Lack of data	13/42 glioblastoma 3/13 anaplastic astrocytoma 0/21 low-grade adult glioma 0/22 childhood glioma
				4	1	
				5	1	
				6	3	
				7	2	
				8	2	
68	Fukushima *et al.* [81]	2006	14/63 (21%)	2	1	Glioblastoma
				5	1	
				6	1	
				7	4	
				8	3	
69	Li *et al.* [82]	2014	1/1 (100%)	7	1	Anaplastic oligodendroglioma
70	Broniscer *et al.* [83]	2009	1/23 (4.3%)	5	1	–

es per 69 (51%) (Figure 8), followed by exon 1 (12 cases – 17%). With respect to exon 5, mutations were most often observed in codons 153, 157, and 159 (3 cases each).

Regarding ovarian cancer, mutations most often concerned exon 5 – 8 cases in the total of 16 (50%), followed by exon 8 – 4 cases (25%) (Figure 9). Mutations in exon 5 most frequently concerned codon 130 (5 cases per 8 – 63%).

With respect to pancreatic cancer, mutations of the PTEN gene were found in 4 per 24 cases (16.7%). Only one study reported the type and site of mutation (Uemura *et al.*) – exon 7, mutation R234Q.

Summing up, in all the malignant tumours analysed in this report, mutations were most often observed in exon 5 – 238 per 488 cases (49%), followed by exon 8 – 72 cases (15%), and exon 7 – 61 cases (13%) (Figure 10).

Discussion

The loss of the PTEN phosphatase function leads to kinase mTOR complex 1 (mTORC1) hyperactivity; hence, it is considered justifiable to include targeted treatment using rapamycin analogues, such as everolimus or temsirolimus. These drugs are mTOR kinase inhibitors [26, 33, 50]. Everolimus is the drug accepted by the U.S. Food and Drug Administration (FDA) for the treatment of advanced neuroendocrine tumours, hormone-dependent breast cancer, and renal cell carcinoma [26]. A study by Kmak *et al.* in 2020 presented a case report describing a 67-year-old patient suffering from hormonal therapy-resistant prostate adenocarcinoma with bone metastases. Tumour material collected after prostatectomy was subjected to genetic testing, which revealed a mutation inactivating the *PTEN*: N323fs*21. In the presented systematic review, mutations of the *PTEN* in prostate cancer were frequently observed – in 41.76% of cases. Oral therapy was introduced with mTOR kinase inhibitor: everolimus 10 mg daily. During treatment stabilization of PSA was obtained, and the progression of the disease stopped. After 3 months the dose was reduced to 5 mg daily due to side effects in the form of weakness and cytopaenia. Treatment with everolimus was discontinued after 8 months due to the progression of the disease [26]. In a study by Elvin *et al.*, targeted treatment was applied in a female patient with the diagnosis of metastasis of ovarian clear cell carcinoma to the liver. Genetic tests of the metastasis confirmed changes within *PTEN* and *PI3K*, which show sensitivity to treatment with everolimus. In our report mutations of *PTEN* in ovarian cancer were found in 5.34% of analysed cases. Treatment with everolimus was in-

Table 2. Summary of mutations of the PTEN gene in malignant tumours

Malignant tumours	Number of tumours with mutation of PTEN	Number of patients examined	Number of tumours with mutation of PTEN/Number of patients examined	Confidence interval (confidence level 95%)
Salivary gland cancer	0	3	0.0000	<0.0000; 0.7080>
Hepatocellular carcinoma	1	102	0.0098	<0.0017; 0.0535>
Colorectal cancer	21	543	0.0387	<0.0254; 0.0584>
Ovarian cancer	18	337	0.0534	<0.0340; 0.0828>
Melanoma	2	36	0.0556	<0.0154; 0.1814>
Breast cancer	52	w773	0.0673	<0.0517; 0.0872>
Gastric cancer	5	71	0.0704	<0.0305; 0.1545>
Lung cancer	18	244	0.0738	<0.0472; 0.1136>
T-cell acute lymphoblastic leukaemia	17	175	0.0971	<0.0615; 0.1501>
Cervical cancer	5	32	0.1563	<0.0530; 0.3280>
Pancreatic cancer	4	24	0.1667	<0.0470; 0.3740>
Glioma	128	590	0.2169	<0.1856; 0.2520>
Uterine sarcoma	2	9	0.2222	<0.0280; 0.6000>
Prostate cancer	38	91	0.4176	<0.3216; 0.5202>
Endometrial cancer	358	730	0.4904	<0.4543; 0.5266>
Cholangiocarcinoma	1	2	0.5000	<0.0130; 0.9870>
Hepatic angiosarcoma	1	2	0.5000	<0.0130; 0.9870>
Germinal tumour of the mediastinum	1	1	1.0000	<0.0250; 1.0000>
Lymphoma	2	2	1.0000	<0.1580; 1.0000>
Follicular dendritic cell sarcoma	1	1	1.0000	<0.0250; 1.0000>
Pancreatic neuroendocrine tumour	1	1	1.0000	<0.0250; 1.0000>
Total	676	3769	0.1794	<0.1674; 0.1919>

troduced at a dose of 10 mg daily. In a PET-CT scan performed after 15 months of treatment no metabolically active cancer was observed. After 27 months of treatment the level of CA-125 remained low. The decision was made to continue treatment with everolimus until the occurrence of adverse effects of treatment or progression of the disease [43].

Temsirolimus is a cytostatic drug inhibiting cell cycle, with anti-cancer properties. Via mTOR kinase inhibition, this drug inhibits the growth of various types of cancer cells and prolongs the progression-free survival and overall survival of patients with renal cell carcinoma. Intermittent drug dosing minimizes its immunosuppressive effect while maintaining its anti-cancer effect. As standard, one 25-mg dose of the drug is administered intravenously once a week. The most frequently observed side effects of temsirolimus are fatigue, rash, inflammation of the mucous membranes, pneumonia, and lymphopaenia. In a phase II clinical trial by Oza *et al.*, temsirolimus was applied in a single dose of 25 mg weekly in patients diagnosed with endometrial cancer. In the presented systematic review endometrial cancer is the cancer best examined for the occurrence of mutations of the *PTEN* – a total number of 730 cases examined, whereas mutation of the *PTEN* was found in 358 cases (49.04%). In a study Oza *et al.* 62 patients were enrolled with recurrent or disseminated endometrial cancer. The patients were divided into 2 groups: Group A – 33 patients in whom chemotherapy was not applied, and Group B – 27 patients who had previously undergone chemotherapy. Cancer tissues of patients from Group A were genetically tested. The sequencing of exons 1, 2, 5, 6, 7, and 8 was performed. Mutations of the *PTEN* gene were observed in 17 patients from this group. A response to the applied treatment in the form of stopping the progression of the disease or an objective response to treatment was obtained in 83% of cases of patients from Group A and 52% of cases from Group B (Figure 11) [50]. An exceptional response to treat-

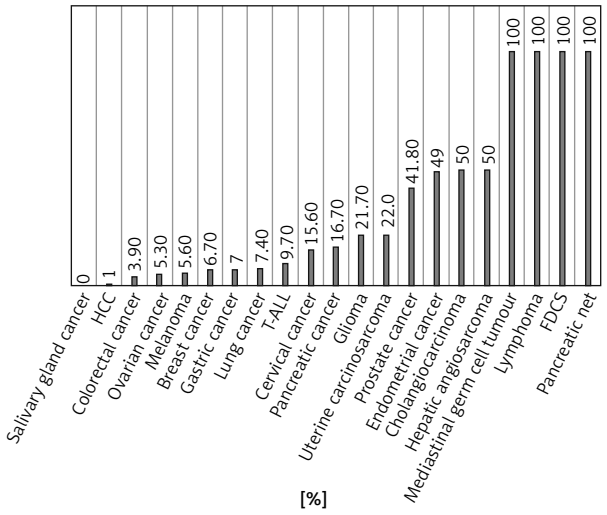

Figure 5. Summary of mutations of the PTEN in malignant tumours

T-ALL – T-cell acute lymphocytic leukaemia, FDCS – follicular dendritic cell sarcoma, HCC – hepatocellular carcinoma, pancreatic NET – pancreatic neuroendocrine tumour.

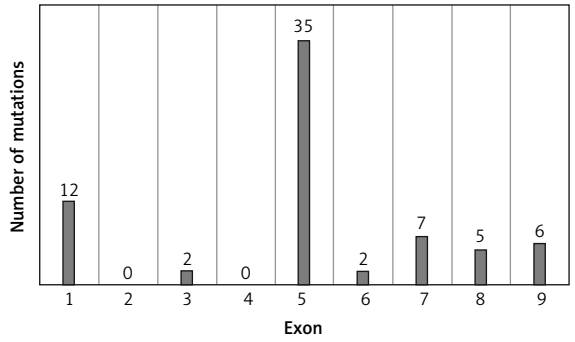

Figure 8. Number of mutations of the PTEN in individual exons in breast cancer

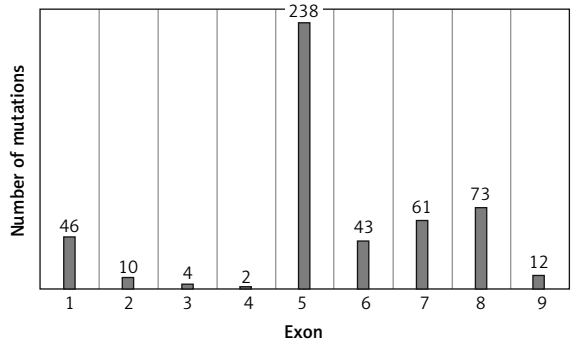

Figure 10. Summary of mutations in individual exons in all malignant tumours

ment with the rapamycin analogue was obtained in a patient with pulmonary adenocarcinoma stage IV with mutation diagnosed within *PTEN* (D268fs30). In the presented study *PTEN* was mutated in 7.38% of

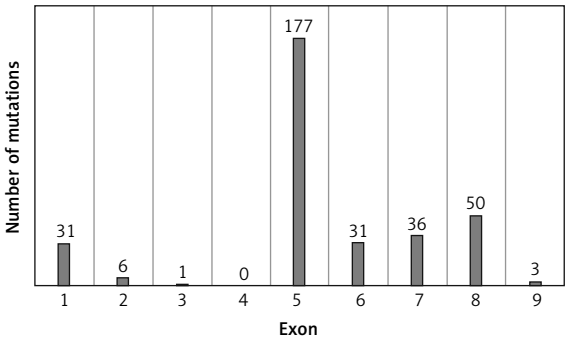

Figure 6. Number of mutations of the PTEN in individual exons in endometrial cancer

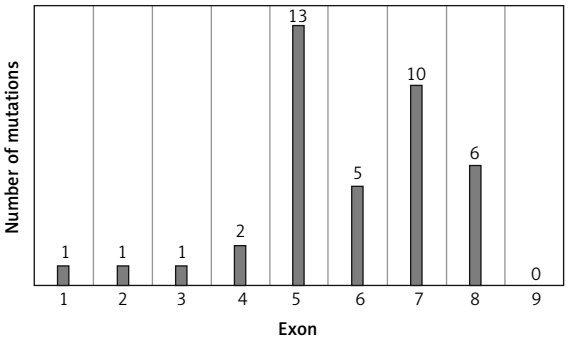

Figure 7. Number of mutations of the PTEN in individual exons in glioma

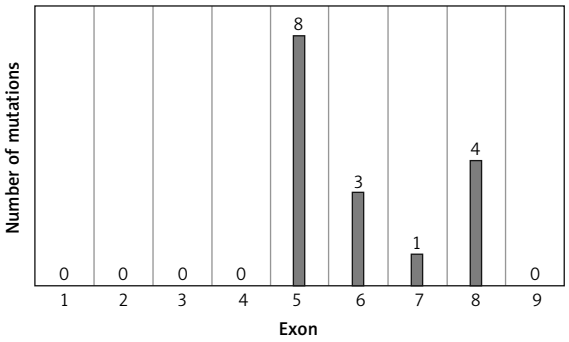

Figure 9. Number of mutations of the PTEN in individual exons in ovarian cancer

cases. Treatment with temsirolimus was introduced at a dose of 25 mg weekly, in accordance with the dosage in renal cell carcinoma. After 3 months of treatment a substantial improvement was observed in the patient's general condition and respiratory efficiency. A considerable shrinkage of the tumour of the left lung and pleura was observed. After 20 months of treatment progression of the disease occurred [33].

In their study Martingetti *et al.* performed genetic analysis of 12 genes from the fluid obtained by washing the uterine cavity in a 67-year-old asymptomatic patient. In histopathological examination of the endometrium no cancer texture and precancerous changes were found. In the material obtained from

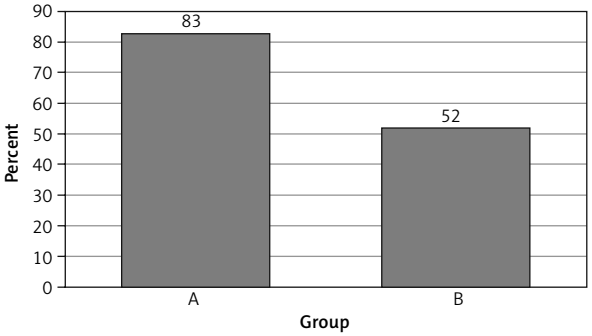

Figure 11. Response to the temsirolimus treatment in endometrial cancer (Group A – patients in whom chemotherapy was not applied, and Group B – patients who had previously undergone chemotherapy) [50]

uterine cavity washings 2 oncogenic mutations of the *PTEN* and other genes: *PIK3CA*, *FBXW7*, and *FGFR2*, were detected. Ten months later the patient reported due to postmenopausal bleeding from the reproductive tract. An endometrial biopsy showed hyperplasia with atypia (precancerous changes) and suspicion of endometrial adenocarcinoma. The patient was qualified for hysterectomy with the removal of appendages. Histopathologic examination confirmed endometrial adenocarcinoma [48].

A special focus of our attention is pancreatic cancer, due to its high mortality and unfavourable prognosis. In recent years the frequency of occurrence of this cancer has been gradually increasing [14]. Compared to other malignant cancers the survival rate in pancreatic cancer has remained relatively unchanged since the 1960s. Pancreatic cancer is usually detected at an advanced stage, when the majority of treatment methods are already ineffective [84]. Hence, pancreatic cancer is an important clinical problem which requires further scientific studies. In the presented scientific review mutations of the *PTEN* gene were detected in 4 per 24 cases of pancreatic cancer (16.7%).

The lack of PTEN expression is due not only to mutation within its gene, but also to epigenetic changes that attenuate the *PTEN* gene [69]. Mutations of the *PTEN* gene are relatively rarely observed in the case of some cancers, e.g. in colorectal cancer they are noted in only 3.9% of cases. In turn, the loss of PTEN protein expression in immunohistochemical examinations is observed considerably more often – in 19–54% of cases. This phenomenon emphasizes the role of alternative mechanisms, such as epigenetic attenuation of the PTEN protein expression [85]. Comprehensive, cohort studies analysing lung cancer specimens showed the loss of the *PTEN* expression in approximately 40% of cases. However, the results of various scientific reports are consistent with respect to the low rate of genetic aberration in the *PTEN* gene (approximately 2–7% of cases). This indicates the background of the regulation of the *PTEN* gene expression other than genetic. Epigenetic (miRNA, methylation and acetylation of DNA) and posttranslational (phosphorylation, oxidation) mechanisms were confirmed which exert an effect on the expression and activity of the PTEN protein. Moreover, it was confirmed that cigarette smoking causes inhibition of the PTEN protein expression in the immunological mechanism. This results in an increased activity of the mTOR/Akt pathway in the respiratory epithelium in smokers, compared to non-smokers [3].

In breast cancer various types of lack of *PTEN* gene expression were observed: loss of heterozygosity, germinal mutations, somatic mutations, and epigenetic attenuation of the *PTEN* gene promoter by its methylation. Also, inhibition of *PTEN* transcription was observed, and degradation and posttranslational modification of the PTEN protein [1]. In the presented review mutations of the *PTEN* gene in breast cancer were observed in 6.73% of the examined cases. Feilotter *et al.* examined in their study 70 cases of sporadic breast cancer. Specimens of tumours and peripheral blood samples were collected. The control comprised 60 blood samples from healthy individuals. In the DNA of 27 tumours the loss of heterozygosity was observed. The sequencing of the genes of these tumours was performed; however, no mutations were detected [20]. In the case of endometrial ovarian cancer, the *PTEN* mutations were observed in 20% of cases, while the loss of heterozygosity was seen in 60 (64% of cases). The rate of mutation of the *PTEN* gene is lower in other types of ovarian cancer: 2% are mutations, and 28% are cases of loss of *PTEN* heterozygosity [37]. In this survey mutations of the *PTEN* gene in the case of ovarian cancer were detected in 5.34% of cases. A study by Lin *et al.* (2015) included 198 patients with colorectal cancer examined for the loss of PTEN protein function. DNA sequencing was performed for exons 1-9 by the Sanger method, and 5 mutations were observed per 198 examined cancers (2.52%). In addition, hypermethylation of the *PTEN* gene was found in 54 (27.3%) cases. In 68 (34.3%) cases the loss of PTEN protein expression was detected. It was confirmed that the loss of PTEN protein expression is associated with the stage of cancer. In stage I cancer the loss of *PTEN* expression was detected in 20% of cases, and in stage IV cancer it was 56.9%. Within 5 years, in 80 (40.4%) patients metastases were diagnosed, while in 42 (52.5%) the loss of *PTEN* expression was seen [67]. In the presented review, mutations of the *PTEN* gene were observed in 3.87% of the analysed cases of colorectal cancer.

Conclusions

Identification of mutations in the *PTEN* gene in malignant tumours is of great clinical importance – targeted treatment with rapamycin analogues is available for patients. The effectiveness of this therapy in the treatment of some malignant cancers has been

clinically confirmed. Sequencing of the whole gene, or only its exons, is associated with high costs. Hence, it is important to identify the most commonly mutated sites of the *PTEN* gene, which would allow quicker and cheaper diagnostics of mutations within this gene and the introduction of targeted treatment with rapamycin analogues. The analysis performed shows that mutations resulting in carcinogenesis most frequently occur in exon 5 – encoding the active centre of the PTEN protein. Further studies are necessary aimed at the identification of mutations of the *PTEN* gene in cancers that have not been properly examined from this aspect.

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Conflict of interest

The authors declare no conflict of interest.

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