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Clinical data analysis with the use of artificial neural networks (ANN) and principal component analysis (PCA) of patients with endometrial carcinoma

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Summary

Aim	Satisfactory performance of modern data processing methods, namely principal component analysis (PCA) and artificial neural network (ANN) analysis, has been demonstrated in the prediction of the results of surgical treatment for endometrial carcinoma.
Materials/Methods	The data from 121 patients treated and observed in one oncology unit was retrospectively evaluated. 26 subject and treatment variables were determined for each patient. A matrix of 121×26 data points was subjected to PCA and ANN processing.
Results	The properly trained ANN was used to predict whether patients belonged to the group of those who survived, or to the group of those who did not survive, a 5-year period. It was found that the prognostic capability of the ANN, regarding the tested set of patients, was very high. Additionally, using the principal component analysis (PCA) method, two principal components, PC1 and PC2 were extracted and accounted, cumulatively, for 23% of the variance in the data analyzed. An apparent clustering of the variables and a clear cut clustering of the patients was observed, which has been interpreted in terms of similarity, or dissimilarity, of the variables and of the patients.
Conclusions	It has been concluded that ANN analysis offers a promising alternative to established methods for the statistical analysis of multivariate data in cancer patients. Also, PCA has been recommended as a new and promising alternative to classical regression analysis of multivariate clinical data. By means of PCA, practically useful systematic information may be extracted from large sets of data, which is otherwise hardly interpretable in comprehensive physical terms. Such information can be of value for general prognosis and for making appropriate adjustments in treatment.
Key words	artificial neural networks (ANN) • principal component analysis (PCA) • endometrial carcinoma • survival model

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BACKGROUND

Endometrial carcinoma is the most common cancer of the female reproductive system in the United States. It accounts for 6% of all female cancers in this country. The general choice of treatment depends on the stage of the disease, hormonal status, and patient age, among others [1]. The therapeutic strategy depends on the prediction of outcome and response to therapy. However, a reliable prediction of the results of treatment is extremely difficult because of the lack of single prognostic parameters or identified combinations of these [2].

Several factors have been recommended to help in the prognosis of both overall survival and the recurrence-free interval in patients with various types of cancer, including cancer of the uterus [3–9]. Endometrial carcinoma is the fifth most common among Polish women and the frequency with which it is diagnosed is rising [10]. According to the new classification of the International Federation of Gynecology and Obstetrics (FIGO) (1988), in order to evaluate the proprietary stage of endometrial cancer maturity, one must perform a total hysterectomy with bilateral salpingo-oophorectomy and peritoneal cytology, as traditionally performed, in addition to a pelvic and para-aortic lymphadenectomy. The appearance of malignant cells in these groups of lymph nodes affects the clinical stage of the cancer and is evidence for likely spread [11,12]. This provides information regarding the spread of the cancer and also decreases the number of women who must subsequently undergo supplementary radiotherapy. The excision of the lymph nodes with metastases has diagnostic as well as therapeutic advantages. However, surgical treatment including lymphadenectomy in older, overweight patients, with additional diseases such as diabetes and hypertension comes with increased risk [13,14]. Hence, it is postulated that it may be of value to individualize the the decision regarding lymphadenectomy, and to broaden the treatment possibilities by means of clinical and histological prognostic factors.

The fundamental problem with multiple regression analyses is that the parameters (independent variables) considered simultaneously cannot be mutually related [15]. To find a representative and, for statistical purposes, sufficiently large set of suitable treatment parameters is difficult. Therefore, prognostic indices derived by means of multiple regression analysis are of rather limited reliability.

Artificial neural network (ANN) analysis is a new method, which aims to emulate the working of the brain. ANNs differ from classical computer programs in that they “learn” from a set of examples, rather than being programmed to get the right answer. The information is encoded in the strength of the network’s “synaptic” connections [16,17]. In chemistry and related fields of research interest, neural-network computing has been described since 1986 [18,19]. ANNs found applications in compound classification, modeling of structure-activity relationships, identification of potential drug targets and the localization of structural and functional features of biomolecules [20–23]. ANNs have been proposed as decision support systems in dentistry [24], in urology [25–27], and to assess HIV/AIDS-related health performance [28].

The general idea of principal component analysis (PCA) is to reduce the dimensionality of the original multivariate data set by finding linear combinations of those variables that best explain the variability within the set of data considered. By means of PCA, systematic information, initially dispersed over a large matrix of input variables (often intercorrelated), is extracted and condensed into a few abstract variables. Projections of data points ascribed to individual objects (patients) and to individual variables reflect mutual similarities and dissimilarities among them [18].

The purpose of this work was to prove that ANN and PCA are convenient and reliable prognostic tools, using the example of surgical treatment

Table 1. Variables considered in an analysis by an artificial neural network (ANN).

No.	Variable name
1	Age (years)
2	Year of surgery
3	Place of residence: Village (0), City (1)
4	Marital status: Widow (0), Married (1), Single (2)
5	Education: Secondary (0), Higher (1), Elementary (2)
6	Professional activity: Pension (0), Employed (1), Unemployed (2)
7	Blood group: A (0), B (1), AB (2), O (3)
8	Number of deliveries
9	Number of miscarriages
10	Age at first menstruation (years)
11	Age at last menstruation (years)
12	Postmenopausal diagnosis: Yes (0), No (1)
13	Obesity: Yes (0), No (1)
14	Arterial hypertension: No (0), Yes (1)
15	Diabetes mellitus: No (0), Yes (1)
16	Endometriosis: Internal (0), No (1), Neoplasia in endometriosis (2), External (3)
17	Uterine myoma: No (0), Yes (1)
18	Scrapings histological type: Adenocarcinoma (0), Hyperplasia atypica end. in carcinoma vertens (1), Adenocarcinoma bene differentiatum end. (2), Adenocarcinoma male differentiatum end. (3), Hyperplasia atypica end. cum atypia gr. maioris (4), Neoplasma malignum (5), Adenocarcinoma mediocriter differentiatum (6) Adenocarcinoma claro-cellulare (7), Absence of cancer cells in pre-operational material (8)
19	Histologic type of post-operational material: Absence of cancer cells in pre-operational material (0), Adenocarcinoma mediocriter differentiatum (1), Adenocarcinoma bene differentiatum end. (2), Adenocarcinoma male differentiatum end. (3), Carcinoma adenosquamosum (4), Adenoacanthoma (5), Carcinoma solidum (6), Hyperplasia atypica end. in carcinoma vertens (7), Hyperplasia atypica end. cum atypia gr. mediocri (8), Adenocarcinoma claro-cellulare (9)
20	Endometrial carcinoma histological grading: G 1 (0), G 2 (1), G 3 (2)
21	Endometrial carcinoma staging: I A (0), I B (1), I C (2), II A (3), III A (4), II B (5), IV B (6), IV A (7), III C (8)
22	Occurrence of other neoplasms: No (0), Malignant (1), Benign (2)
23	Kind of applied surgical treatment: Total abdominal hysterectomy with bilateral salpingo-oophorectomy (0), Total abdominal hysterectomy with bilateral salpingo-oophorectomy + peritoneal cytology (1), Total abdominal hysterectomy (2), Amputation of the body of the uterus with bilateral salpingo-oophorectomy (3), Total abdominal hysterectomy with bilateral salpingo-oophorectomy + peritoneal cytology + pelvic and paraortic lymphadenectomy (4)
24	Depth of myometrial invasion: Limited to endometrium (0), < 1/2 muscle thickness (1), > 1/2 muscle thickness (2)
25	Vascular space invasion: No (0), Yes (1)
26	Colpitis: No (0), Yes (1)
Class	Category: Did not survive 5 years after operation (0), Survived 5 years after operation (1)

results in endometrial carcinoma. By this method, one can exploit all of the available information on a patient, disease and treatment, making use of a single analysis of the variables ranging from sociology to genetics. In this project the ap-

proach was tested on the material available for 121 endometrial carcinoma patients who were treated and observed in the Surgical Gynaecology Department of the Specialist Provincial Hospital in Olsztyn.

Table 2. Variables considered in an analysis by an artificial neural network (ANN) and their values for six exemplary patients.

Variable No.	Variable Name	Variable value for patient					
		No. 1	No. 2	No. 3	No. 4	No. 5	No. 6
1	Age (years)	54.6	63.9	44.2	37.9	74.8	79.7
2	Year of surgery	1988	1991	1989	1995	1994	1994
3	Place of residence	1	1	1	0	1	1
4	Marital status	0	1	2	1	2	0
5	Education	2	2	2	2	2	2
6	Professional activity	1	1	1	0	0	0
7	Blood group	3	1	1	1	0	0
8	Number of deliveries	2	1	1	1	1	5
9	Number of miscarriages	0	0	1	0	3	1
10	Age at first menstruation (years)	12	11	14	17	14	13
11	Age at last menstruation (years)	54	56	44	32	51	56
12	Post menopausal diagnosis	0	1	0	1	1	1
13	Obesity	1	1	0	1	0	0
14	Arterial hypertension	0	1	0	1	0	0
15	Diabetes mellitus	0	0	0	1	0	0
16	Endometriosis	1	1	1	2	1	1
17	Uterine myoma	0	0	0	0	1	0
18	Scrapings histological type	2	0	0	0	0	0
19	Histological type of post-operational material	1	1	2	9	1	1
20	Endometrial carcinoma histological grading	1	1	0	2	1	1
21	Endometrial carcinoma staging	1	1	1	6	2	5
22	Occurrence of other neoplasms	0	0	0	1	0	0
23	Kind of applied surgical treatment	0	0	0	4	4	1
24	Depth of myometrial invasion	1	1	1	1	2	1
25	Vascular space invasion	0	0	0	1	0	0
26	Colpitis	0	0	0	1	1	1
27	Category	1	1	1	0	0	0

MATERIALS AND METHODS

Patients

Data on 121 patients with endometrial carcinoma was retrospectively collected and analyzed. The variables considered in this study are presented in Table 1. A total number of 26 variables were subjected to ANN and PCA analyses. The final matrix of data subjected to ANN and PCA

analysis therefore consisted of 121 patients multiplied by 26 variables. Table 2 presents the data for six selected patients: surviving or not surviving a 5-year period after surgical treatment.

ANN analysis

Artificial neural networks (ANN) were run on a personal computer using Statistica Neural Networks software (StatSoft, Tulsa, OK, USA).

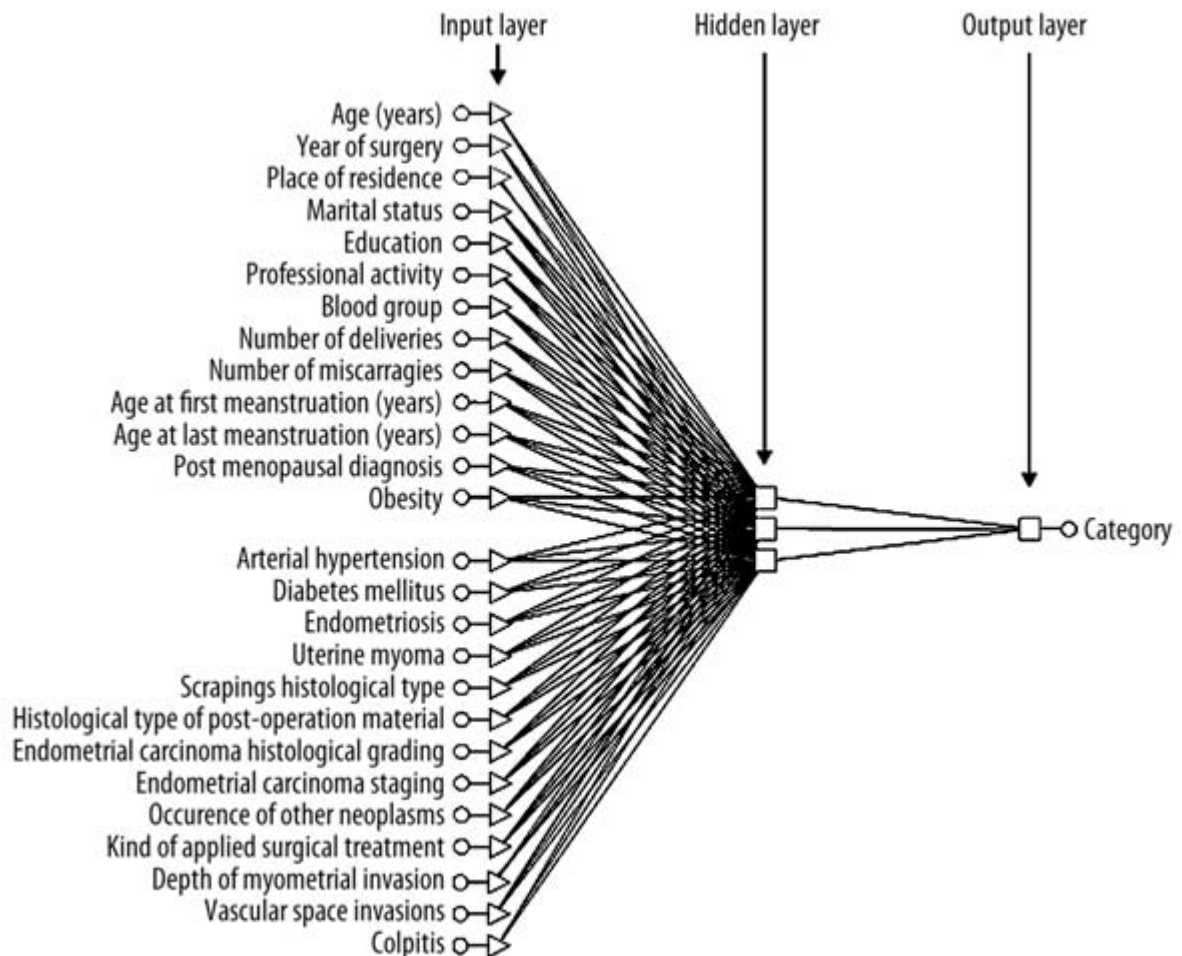


Figure 1. Architecture of the artificial neural network used in predictions of survival in cases of endometrial carcinoma.

An artificial neural network based on a multi-layer perceptron and consisting of 26 artificial neurons in the input layer, 3 in a hidden layer and 1 in the output layer was used. The architecture of the model utilized is depicted in Figure 1. A supervised method of training with a back-propagation strategy was used. Variables from the patients analyzed were divided into three sets: a training set with 71 patients, a validating set with 25 patients and a testing set with 25 patients. Training the ANN was executed through 3000 epochs, and the learning coefficient was 0.1; momentum equaled 0.3. Data from the training set was presented in a randomized manner during the training process. The changes in RMS error were recorded for the training and validating sets during the training process (Figure 2). For further considerations, one takes the artificial neural network with the lowest RMS error, with regards to the validating set of data. In this case, teaching the network was completed in 1557 epochs.

PCA analysis

Principal component analysis of the 121×26 data matrix was performed by means of the *Statistica* computer program (StatSoft Inc, Tulsa, OK, USA), operated on a personal computer. It was found that two first principal components, PC1 and PC2, cumulatively accounted for 23% of the total variance in the data described by 26 original variables.

The projection of points assigned to individual patients (principal component "scores") in the space determined by the first two principal components axes, PC1 and PC2, is depicted in Figure 3.

The variables positioned in the space determined by the first principal components produce a plot of principal component "loadings". The principal components most significant for separation of patients ("object scores") in Figure 3 are PC1 and

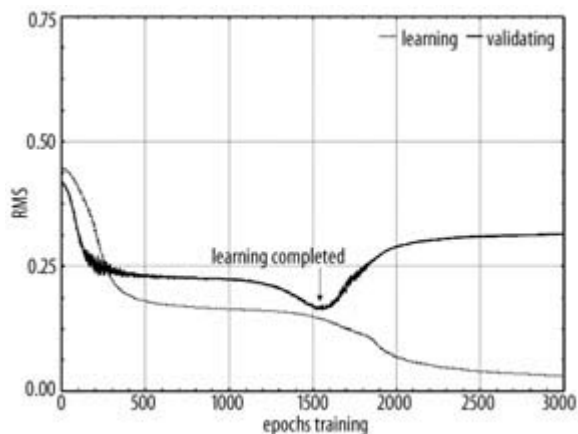


Figure 2. Training Error Graph.

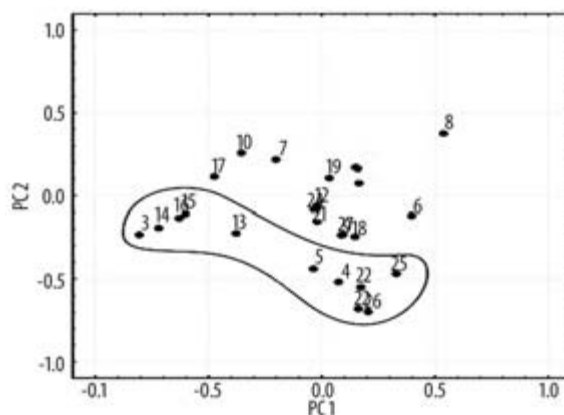


Figure 4. A projection of 26 variables from Table 1 on the plane of PC1 and PC2 from a principal component analysis (PCA) of data for 121 patients.

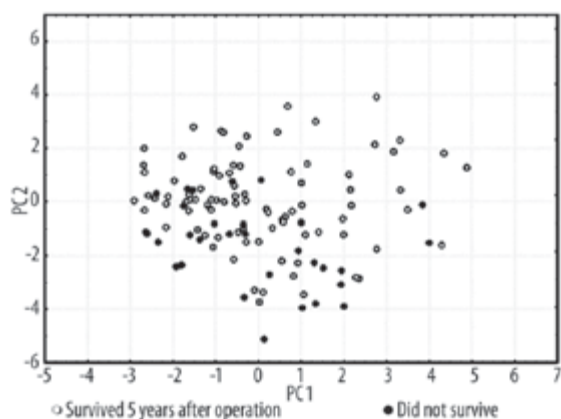


Figure 3. A projection of 121 points denoting patients (described by 26 variables listed in Table 1) in the space of the first two principal components, PC1 and PC2, and derived from a principal component analysis (PCA) of a 121x26 data matrix.

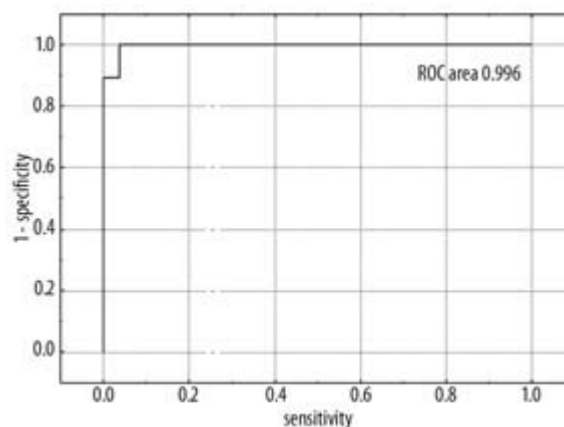


Figure 5. Receiver Operating Characteristic curves (ROC curves) for the training set.

PC2. Therefore in Figure 4 the “loadings” of PC1 and PC2 by individual variables are presented.

RESULTS AND DISCUSSION

Figure 1 presents the architecture of the ANN model used for predictions of 5-year survival of cancer patients, based on the input data from the training, validating and testing data sets, respectively.

In Table 3, classification statistics are collected for training, validating and testing sets and in Table 4 correlations between the variables considered, correlations between PCs and analyzed variables, are presented. A summation of the princi-

pal component analysis is demonstrated in Table 5. Receiver Operating Characteristic curve (ROC curve) for the training set is shown in Figure 5.

By using the proposed method, it was possible to differentiate the patients in the testing group as cases of survival or non-survival with no error. The prognostic potency of the ANN, with regard to the set of test patients, is excellent and proves a good choice of network and its form. All patients in the testing set, of total number of 25, were correctly classified, which means that one is able to predict the survival of patients with endometrial carcinoma, utilizing the selected variables, with very high probability.

Table 3. Classification statistics.

	Training set		Validating set		Testing set	
	Lived	Died	Lived	Died	Lived	Died
Total	52	19	19	6	20	5
Correct	50	18	18	6	20	5
Incorrect	2	1	1	0	0	0
Lived	50	1	18	0	20	0
Died	2	18	1	6	0	5

Table 4. Correlations between PCs and analyzed variables.

	Variable No.												
	1	2	3	4	5	6	7	8	9	10	11	12	13
PC 1	-0.806	0.074	-0.037	0.397	-0.203	0.538	0.093	-0.355	0.164	-0.019	-0.378	-0.720	-0.604
PC 2	-0.233	-0.518	-0.438	-0.119	0.217	0.376	-0.231	0.257	0.074	-0.067	-0.225	-0.192	-0.110
PC 3	-0.045	0.050	0.586	0.023	-0.465	0.211	0.125	-0.446	-0.304	-0.390	0.257	-0.082	0.119
PC 4	0.001	-0.659	0.092	0.077	0.112	-0.005	0.300	-0.057	0.092	-0.117	0.317	-0.047	-0.137
PC 5	0.002	-0.203	0.335	0.287	-0.384	0.148	-0.106	-0.240	0.208	-0.004	0.220	0.172	-0.156
PC 6	0.106	-0.125	0.134	-0.461	0.209	-0.005	-0.431	-0.262	-0.290	0.217	0.101	0.075	-0.277
PC 7	-0.010	0.086	0.095	0.055	0.030	0.083	0.079	-0.183	-0.504	-0.267	-0.184	0.140	0.120
PC 8	0.073	0.147	0.300	-0.194	-0.278	-0.006	-0.211	-0.023	-0.011	0.447	0.076	-0.080	-0.316
PC 9	0.137	-0.163	-0.003	-0.121	-0.307	0.248	0.437	0.092	-0.232	0.102	-0.291	0.201	0.112
PC 10	0.063	-0.144	0.128	-0.381	-0.149	-0.118	-0.112	-0.181	0.445	-0.432	-0.161	0.013	0.034
PC 11	0.129	-0.025	-0.052	0.225	0.128	-0.174	-0.021	-0.304	-0.110	0.240	-0.335	0.384	-0.080
PC 12	0.091	0.139	0.088	-0.205	0.309	-0.105	0.215	-0.089	-0.135	-0.248	0.287	-0.050	-0.098
PC 13	0.096	-0.049	0.151	0.117	0.169	-0.181	0.427	-0.223	0.322	0.156	-0.144	0.020	0.001
PC 14	0.086	0.078	-0.077	0.079	0.019	-0.132	0.056	0.224	0.128	-0.232	0.156	0.192	-0.404
PC 15	0.042	-0.069	0.009	-0.327	-0.202	-0.051	0.250	0.204	-0.062	0.212	0.007	-0.072	-0.083
PC 16	-0.256	0.020	-0.074	-0.144	-0.174	-0.411	0.074	-0.073	0.010	0.021	-0.132	-0.041	-0.188
PC 17	-0.114	0.081	0.063	0.029	-0.018	-0.001	-0.028	0.237	-0.040	-0.076	-0.033	0.006	0.116
PC 18	0.052	-0.082	0.051	-0.193	0.002	0.037	0.075	0.112	-0.085	-0.155	-0.285	-0.056	-0.070
PC 19	0.145	-0.057	0.132	-0.008	0.009	0.138	-0.212	0.045	0.162	-0.061	-0.208	0.186	-0.061
PC 20	-0.126	-0.098	0.145	0.036	0.058	-0.323	-0.152	-0.019	-0.092	-0.029	-0.136	-0.173	0.202
PC 21	0.006	0.086	0.183	0.181	-0.086	-0.131	-0.018	0.247	-0.073	-0.077	-0.066	0.058	-0.129
PC 22	-0.128	0.028	-0.017	-0.041	0.140	0.064	0.034	-0.077	-0.105	-0.117	-0.106	0.096	-0.215
PC 23	0.138	0.005	0.055	-0.014	-0.002	0.004	-0.028	0.038	0.071	-0.065	-0.085	-0.101	0.062
PC 24	-0.077	-0.095	0.282	0.007	0.225	0.070	0.042	0.127	0.006	0.107	-0.010	-0.047	-0.021
PC 25	-0.040	-0.280	-0.041	0.064	-0.069	-0.079	-0.044	0.029	-0.095	-0.022	0.073	0.075	-0.016
PC 26	-0.222	0.040	0.042	-0.093	0.003	0.026	0.012	0.024	0.076	0.017	0.038	0.202	0.098

Table 4 cont. Correlations between PCs and analyzed variables.

	Variable No.												
	14	15	16	17	18	19	20	21	22	23	24	25	26
PC 1	-0.630	-0.475	0.147	0.034	0.148	-0.021	0.173	0.162	-0.033	0.329	0.203	0.087	0.162
PC 2	-0.133	0.115	-0.245	0.105	0.171	-0.153	-0.549	-0.681	-0.084	-0.469	-0.699	-0.236	0.160
PC 3	0.104	0.077	0.147	0.462	0.093	0.373	-0.300	-0.366	0.124	0.136	-0.388	0.132	-0.343
PC 4	-0.081	-0.124	-0.314	0.143	-0.190	0.203	0.263	0.153	-0.130	-0.585	0.150	0.591	-0.088
PC 5	0.245	-0.068	-0.118	-0.033	-0.532	-0.632	-0.092	0.078	0.168	-0.129	-0.014	-0.391	0.340
PC 6	-0.299	-0.297	0.201	-0.025	-0.019	-0.129	0.233	-0.168	0.397	-0.179	0.085	-0.144	-0.320
PC 7	0.163	-0.412	-0.358	-0.473	0.177	-0.186	0.174	-0.141	-0.376	-0.061	-0.065	-0.014	-0.004
PC 8	-0.046	0.274	-0.567	-0.024	0.304	0.194	-0.056	0.035	-0.198	-0.054	0.087	-0.021	0.181
PC 9	-0.139	0.090	0.107	-0.137	0.198	0.083	0.069	0.033	0.504	-0.150	0.056	0.025	0.375
PC 10	0.039	0.078	0.227	0.051	0.437	-0.179	0.191	0.083	-0.212	-0.115	0.060	-0.055	0.122
PC 11	-0.067	-0.045	0.053	0.515	0.070	-0.164	-0.045	-0.088	-0.184	0.060	-0.019	0.222	0.191
PC 12	-0.403	0.133	-0.028	-0.018	-0.140	-0.079	-0.078	0.030	-0.071	0.147	-0.139	-0.019	0.416
PC 13	-0.149	-0.016	-0.137	-0.118	0.047	0.100	0.008	-0.111	0.037	-0.006	-0.107	-0.379	-0.273
PC 14	0.154	-0.360	-0.160	0.093	0.268	0.060	-0.097	-0.044	0.288	0.129	-0.017	0.009	0.049
PC 15	0.085	-0.367	0.198	0.149	-0.157	0.046	-0.079	0.052	-0.335	0.024	-0.086	-0.146	0.032
PC 16	0.138	0.137	0.003	-0.182	-0.197	-0.039	0.141	-0.254	0.112	0.057	-0.161	0.236	0.033
PC 17	-0.062	0.020	-0.178	0.329	-0.068	0.027	0.510	-0.090	0.037	0.001	-0.111	-0.215	0.049
PC 18	-0.032	0.112	-0.259	0.133	-0.121	-0.240	-0.143	0.194	0.078	0.179	0.077	0.055	-0.272
PC 19	-0.088	-0.075	0.006	-0.160	-0.221	0.280	0.051	0.094	-0.040	0.137	-0.254	0.101	0.049
PC 20	0.009	-0.172	-0.066	0.042	0.015	0.137	-0.173	0.197	0.150	-0.089	-0.019	-0.083	0.163
PC 21	-0.203	0.069	0.159	-0.062	0.011	-0.067	-0.068	-0.028	-0.091	-0.210	0.025	-0.000	-0.098
PC 22	0.195	0.141	0.062	0.041	-0.097	0.210	-0.021	0.049	-0.044	-0.121	0.148	-0.192	0.036
PC 23	-0.021	-0.069	-0.039	0.013	-0.124	0.065	-0.050	-0.314	-0.007	0.038	0.299	0.019	0.090
PC 24	0.165	0.033	0.094	-0.030	0.089	-0.083	0.035	-0.055	0.015	0.107	-0.017	0.079	0.053
PC 25	-0.069	0.068	0.017	-0.046	0.050	0.050	0.016	-0.028	-0.067	0.211	0.074	-0.106	-0.011
PC 26	-0.077	-0.044	-0.045	-0.001	-0.012	0.001	-0.080	-0.024	-0.006	0.000	0.070	0.028	-0.017

Principal component analysis also extracts systematic information on the variables considered. The most interesting are variables directly connected with a negative prognosis for 5 year post-operative survival: variable numbers: 3, 4, 5, 13, 14, 15, 16, 22, 23, 25 and 26. These variables are located on the left side of Figure 4. Lower values for patients' PC1 and PC2 (closed circles in Figure 3) suggest that deterioration regarding surviving prevails among these patients. On the basis of that analysis it could be assumed that variable numbers: 3, 4, 5, 13, 14, 15, 16, 22, 23, 25 and 26 have significant influence on patients' 5 year post-operative survival. These

take into account variables such as place of residence, marital status, level of education, obesity, the coexistence of arterial hypertension, diabetes mellitus, endometriosis, colpitis or neoplastic diseases other than endometrial cancer, as well as information regarding any kind of surgical treatment applied, or vascular space invasion.

CONCLUSIONS

The presented study is the first ever application of ANN and PCA to endometrial carcinoma outcome prediction. It is mostly methodological in

Table 5. Summation of the principal component analysis.

No. of principal component	Eigenvalue	Variance accounted for (%)	Total variance accounted for (%)
1	3.242	12.470	12.470
2	2.663	10.242	22.712
3	2.098	8.071	30.783
4	1.748	6.722	37.504
5	1.710	6.578	44.082
6	1.417	5.451	49.533
7	1.274	4.900	54.433
8	1.205	4.636	59.069
9	1.149	4.417	63.486
10	1.088	4.185	67.671
11	0.987	3.794	71.466
12	0.845	3.249	74.714
13	0.801	3.080	77.795
14	0.768	2.954	80.748
15	0.704	2.706	83.454
16	0.651	2.505	85.959
17	0.583	2.244	88.203
18	0.539	2.073	90.276
19	0.495	1.902	92.178
20	0.464	1.787	93.965
21	0.343	1.319	95.284
22	0.337	1.297	96.581
23	0.282	1.084	97.664
24	0.260	1.001	98.666
25	0.203	0.782	99.448
26	0.143	0.552	100.000

character and concerns a limited number of cases. It may help to identify a combination of factors providing effective treatment and good prognosis. Furthermore, the ANN and PCA analyses allow for testing a practically unlimited number of either mutually related or apparently unrelated factors and cases.

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