Prediction of Nodal Metastasis and Prognosis of Breast Cancer by ANN-based Assessment of Tumour Size and p53, Ki-67 and Steroid Receptor Expression

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Abstract. Background: Tumour stage and the appropriate course of treatment in patients with breast cancer are primarily characterized by the state of metastasis in the axillary lymph nodes. In recent years, substantial research has focused on the prediction of lymph node status based on various pathological and molecular markers in order to obviate the necessity to carry out axillary dissection. In the present study, artificial neural network (ANN) is employed as the analysis platform to examine the prognostic significance of a group of well-established prognostic markers for breast cancer outcome prediction in terms of nodal status. Furthermore, we investigated existing interactions between these markers. Patients and Methods: The data set contained 66 patient records, where 5 pathological and molecular markers including tumour size, oestrogen receptor status (ER), progesterone receptor status (PR), Ki-67 and p53 expression had been assessed for each patient. The spread of metastasis to the axillary lymph nodes was clinically diagnosed and patients were accordingly categorized into node-positive and node-negative groups. The aforementioned markers were analyzed using a probabilistic neural network (PNN) for nodal status prediction which was considered as the network output. Furthermore, the interactions between these markers were evaluated using different marker combinations as the network input for finding the best marker arrangement for nodal prediction. Results: The best prediction accuracy was obtained by a 3-marker combination including tumour size, PR and p53 with 71% accuracy for nodal prediction. Leaving out ER and PR from the full marker set showed approximately the same variations in the results, which is an indication of the direct correlation of these two markers. Furthermore, tumour size was proved to be the most significant individual marker for predicting nodal metastasis. However, when used in combination with Ki-67 the prediction results drop significantly. Conclusion: The results presented here indicate that molecular and pathological markers can provide useful information for early-stage prognosis. However, the interactions between these markers must be considered in order to achieve accurate and reliable prediction.

Breast cancer remains the major cause of cancer death amongst women. A report by Ferlay and colleagues indicates breast cancer as the most prevalent cancer among Europeans in 2008, afflicting 464,000 people and hence comprising 13.5% of all cancer cases (1). However, in spite of the increase in the number of breast cancer patients, there has been a decrease in breast cancer mortality rate. This is mainly due to applying systemic treatment and surgery in early stages of the disease and also improvement in early-stage prognosis. However, early-stage therapy is undesirable as many patients might undergo unnecessary treatment due to incorrect prognosis (2). So it’s important not to apply unnecessary treatment but at the same time early diagnosis is essential for successful management through adjuvant therapies and surgery.
Among the various approaches to improving diagnosis, several involve defining the state of metastasis in axillary lymph nodes which is an important factor in predicting prognosis and is commonly used for tumour staging. The spread of breast cancer usually starts with metastasis to the regional lymph nodes and therefore the state of lymph node metastasis can provide information useful for determining adjuvant therapy. Sentinel lymph node biopsy (SLNB) is currently the most prevalent technique in defining nodal status. It reduces unnecessary lymph node dissection and is also helpful in detecting micro-metastases. Wong et al. concluded that the low detection ratio of nodal metastasis based on histological type of the tumour necessitated SLNB for all types of breast carcinoma (3). However, SLNB sometimes fails to detect lymph node metastasis and besides, it is only beneficial to patients with positive nodes. Therefore, an alternative method for nodal status prediction is sought by many researchers.

Various tumour attributes are being proposed as being able to provide helpful information in nodal status prediction and molecular markers might be especially advantageous in such systems. However, there has been little agreement to date on a single or a combination of such markers for accurate nodal metastasis prediction that can replace the conventional techniques such as axillary dissection or SLNB (4).

Comprehensive studies such as the one conducted by Esteva et al. have established that hormone receptors and proliferation markers like Ki-67 are valuable as prognostic markers (2). Female steroid hormones, oestrogen and progesterone, promote tumour growth by activating their respective nuclear receptors. The association of oestrogen with breast cancer has been confirmed by several studies and in some studies it has been considered even as the most important factor affecting breast cancer management (5-8).

Oestrogens stimulate the growth of a variety of target tissues through binding to specific nuclear receptors, the oestrogen receptors (ER), which results in ER phosphorylation, conformation modification and hence dimerization. The receptor complex initiates the transcription of responsive genes by binding to the gene promoter region and hence results in appropriate physiological function. Progesterone is also known to influence the function of different homeobox transcription factors in breast cancer cells. Therefore, it could be also inducing the transcription of specific target genes associated with cell proliferation and differentiation. Clarke et al. emphasize that the dependence of breast tumour proliferation on these steroid hormones makes them important factors for cancer prognosis (9). There has also been controversy about which of the steroid hormones, oestrogen or progesterone, is more correlated with breast cancer. In this study, we aim to find the underlying correlation between these two markers and also their prognostic significance in nodal status both individually and together.

Ki-67 is a protein antigen detected using immunocytochemistry (IHC) methods. It is expressed in cell nuclei throughout all active phases of the cell cycle (i.e. G1, G2, S and mitosis) but not in resting G0 cells and also present in both normal and cancerous cells. Thus, Ki-67 is widely recognized as a proliferation marker employed as an indicator of the growth fraction of a tumour cell population and is thus highly effective for predicting the development of tumours (10-12). Different studies concur upon the correlation of high levels of Ki-67 with aggressive tumours and poor prognosis (short survival) (13). Even so, patients with high Ki-67 levels, benefit from chemotherapy as it targets cells with abnormal growth rate. A comprehensive review conducted by Gerdts indicates that determining the growth fraction by Ki-67 is not only of high diagnostic value, but also can be used as an independent prognostic indicator (14). However, Van Oijen and colleagues found that Ki-67 expression is also likely to occur in non-proliferating cells and therefore they recommend using this marker in combination with p53 for more accurate prognostic evaluation (15).

As a tumour suppressor gene, p53 controls cell proliferation when DNA is damaged until DNA is repaired or apoptosis occurs. p53 mutation takes place in more than half of all tumours and it is the most mutated tumour suppressor gene in human tumours (16-17). Therefore, p53 is a significant factor in preventing cancer development and is frequently employed as an important predictive factor in breast cancer (18). P53 accumulation is frequently associated with shorter survival (19, 20). Nevertheless, Vagunda et al. concluded that p53 despite its mutation in the majority of carcinomas, does not always control apoptosis (12). Although the prognostic significance of p53 for survival in early breast cancer has been confirmed by different studies, its positive impact on nodal status prediction is not yet confirmed (22).

Despite discovering a myriad of molecular and pathological markers proving to be valuable in prognosis, there are still shortcomings in predicting prognosis of cancer. This is mainly due to the non-linear relationship between markers and disease outcome which makes it an arduous task for clinicians to accurately predict prognosis based on these markers. Therefore, the need for exact statistical data in this matter is evident.

To address this issue, a wide range of studies have investigated various statistical and artificial intelligence methods for the prediction of nodal involvement exploiting the ever-increasing number of biomarkers deemed to be effective in disease dissemination and metastasis. It is known that the performance of artificial neural networks (ANNs) provides a powerful method of analyzing the inherently complex nature of potential cancer proliferation markers (23). The ability of ANNs to identify highly non-linear relationships occurring between markers makes it a valuable tool in evaluating tumour dissemination and proliferation data.
ANNs are a group of pattern classifiers capable of predicting the outcome of future observations using patterns learned from past examples. The design of ANNs is inspired by the structure of biological neural networks in that they are composed of a large number of interconnected processing units (neurons) working in a parallel manner. This structure makes ANNs a valuable classification tool capable of extracting highly complex patterns in data. However, the processing rate, size, complexity level and the fault tolerance of the ANN is not comparable to biological neural networks.

The basic units of ANNs, the artificial neurons (nodes) simulate four important components of a biological neuron namely synapses, dendrites, cell body and axon. The synapses are represented as weights which define the strengths of the connection between nodes. The dendrites and axon are modelled as the actual activity taking place in ANN neurons, where all the inputs are linearly combined by being weighted and summed up. Finally, the neuron output is computed by passing the linearly-combined inputs through an activation function. Hence, an artificial neuron can be considered as a simplified biological neuron in that it has the ability to predict the output for new data by learning from previous data.

An ANN consists of several neurons arranged in form of distinct layers linked together through weighted connection. ANNs have different names and architectures depending on the way they learn the input/output relationship (training) and also the connection structure of their neurons. The most common type of training is supervised training in which a training dataset including examples of inputs together with the corresponding outputs is used for training the network.

One type of supervised networks is feedforward neural networks in which neurons are connected only in a forward manner and no feedback loop exists. Multilayer perceptrons (MLP) are a class of feedforward networks which consist of three types of layers. The first layer is always an input layer through which the input data are fed into the network. This layer is then connected to hidden layer(s) which are so designated as their output is fed into another hidden or an output layer and hence cannot be directly accessed. Final layer is an output layer which provides the network outcome. MLPs are trained in a supervised manner in which the network connection weights are adjusted by minimizing an error function over training data. This enables the network to predict the outcome for new data using adjusted weights.

Another class of supervised networks is the probabilistic neural network (PNN) which is composed of four layers – input, pattern, summation and output layer (24, 25). PNNs perform a classification task by estimating the probability density function (pdf) of each class in input data using a Parzen window density estimation (26). This enables the network of classifying a new observation by comparing the probabilities of the input belonging to each class and assigning the observation to the most probable class.

An ANN is trained and validated using two non-overlapping groups of data, the training and test sets. The training set is employed for adjusting the weights during training which can be compared with the process of learning in a biological neural network. In ANNS however, the training algorithm consists of building a predictive model that minimizes error when the network’s output is compared with the desired target. The process of utilising the desired target values for training the network is called supervised learning.

Afterwards, the competency of the achieved ANN is validated by the test set in which a part of data, not seen by the ANN before, is used as the input of the ANN and the outcomes of the network is compared with the desired outputs. Hence, the network’s performance in terms of success in arriving at a correct prediction would be evaluated and regarded as the network’s accuracy.

In the present study, we have used an MLP and a PNN as classification platforms to predict for axillary lymph node metastasis in a group of patients with breast cancer. Tumour size together with four unique biomolecular markers, ER, PR and p53, Ki-67 expression, obtained by minimally-invasive methods, were used in terms of their predictive significance associated with metastasis to axillary lymph nodes. In addition, different combinations of these markers in the form of one, two, three and four member sets were considered to find the most effective individual marker or combination set in nodal status prediction. Another objective of evaluating the different marker combinations was to discover the existing non-linear interrelations among them. Although, the correlation between some of these markers and nodal metastasis is well-established in medical literature, there is little detail available on the degree of effectiveness of combining these features for nodal metastasis prediction in breast cancer.

Patients and Methods

The data set used in this study includes 110 patients for whom the five clinical and pathological factors are defined. The results in terms of the number of involved nodes are also included for each patient. These markers along with their attributes and the number of available cases for each factor are listed in Table I. There are some missing or unknown data for some of the markers in the data set which affects the actual number of samples that can be used for training and testing the network.

The patient data set also included tumour stage. Tumour staging is a procedure that has evolved over many years, and has proved to be invaluable to the clinician in the management of patients in terms of disease evaluation and determining adjuvant treatments and assessment of prognosis. A widely-employed standard method for staging breast cancer is TNM staging. Quite obviously, since TNM staging involves surgical procedures and histological assessment of the dissected nodes for the presence of the tumour, tumour staging would be deemed as an invasive procedure and besides it is associated with much morbidity. Hence it has not been included in the analyses here.
The original diagnosis results of nodal involvement provided the number of positive nodes over the number of nodes tested for each patient. We have considered all patients with at least one positive node as having nodal metastasis regardless of the number of nodes tested and only the patients with no positive node are deemed to be free of metastasis.

The ultimate data set used for the study consists of 66 patients’ records, among those 36 were diagnosed as free of metastases and 30 had nodal metastasis. This would be 55% and 45% node-negative and -positive patients respectively in the data set; this implies a reasonable balance between positive and negative cases in the data. This balance is important in output interpretation in terms of positive predictive and negative predictive rates as these values depend on the prevalence of normal and cancer cases in the considered population. Therefore, we can use positive predictive and negative predictive rates as reliable indicators of correctly predicted positive and negative test results respectively.

To allow the evaluation of the effect of different marker combinations and the assessment of interactions between these markers, we have employed a full factorial design considering every possible combination of the markers. Therefore, the experiment involved 31 different combinations including one, two, three and 4-marker groups as well as a combination including all the available markers.

MLP. MLP is a feedforward ANN in which the data, entered at the input layer, propagates in one direction through the hidden layer(s) until it reaches the output layer (Figure 1). In this work, the scaled conjugate gradient algorithm (SCG) is employed for training the network. SCG is an effective approach to perform supervised learning in feedforward MLPs (27). The algorithm consists of a forward and backward step. In the forward pass, the predicted outputs \( O_j \) corresponding to the given inputs of the layer \( y_h \) are evaluated using:

\[
o_j = \phi(\sum_{h=0}^{l} w_{jh} y_{hp}) \tag{Equation 1}
\]

where the output layer’s input \( y_{hp} \) is a vector of outputs of the hidden layer for the \( p^{th} \) input pattern, computed as:

\[
y_{hp} = \phi(\sum_{l=0}^{m} w_{ih} x_{ip}) \tag{Equation 2}
\]

where \( x_{ip} \) is the \( i^{th} \) element of the \( p^{th} \) input pattern, and \( w_{ih} \) and \( w_{jh} \) are the connection weights linking the hidden input- and the hidden output layers respectively. The function \( \phi \) is the non-linear activation function (transfer function), considered, as a hyperbolic tangent sigmoid function in both hidden and output layers and hence represented with the same symbol for both layers:

\[
\phi(y) = \frac{e^{2y} - 1}{e^{2y} + 1} \tag{Equation 3}
\]

This function is used due to its special characteristics such as monotonicity and symmetrical output.

When the forward pass is completed, an error signal is computed by comparing the network’s outputs \( o_j \) with the desired response \( t_j \). The error signal is then fed into a cost function to control the adjustments to the weights. Mean square error (MSE) is commonly used as the cost function which is drawn from maximising the likelihood of each data point \( (x_{ip}, t_{ip}) \) in the training data (28) defined as:

\[
\varepsilon = \frac{1}{2N} \sum_{p=1}^{N} \sum_{j=1}^{m} (t_{jp} - o_{jp})^2 \tag{Equation 4}
\]

which is the mean of squared-error loss over the total number of patterns denoted by \( N \). \( t_{jp} \) and \( o_{jp} \) are the desired output and the network’s output respectively, resulting from the \( p^{th} \) input neuron using the \( p^{th} \) input pattern.

In the backward pass, second partial derivatives of the cost function with respect to the network parameters, weights and biases, are computed and propagated back through the network. Network weights and biases are then updated such that the cost function is minimized. This process is reiterated several times and the training completes when the system reaches the prescribed accuracy or a maximum number of iterations. These two stopping criteria are employed in conjunction to avoid overfitting and to have a sound generalization.

During the test process, test samples whose outputs are unknown to the network are fed to the input layer and the network’s classification outcome is computed using equations 1 and 2. The output would be in the range [-1 1] as the output neuron’s transfer function is a hyperbolic tangent bounded to the range [-1 1]. The outputs in the range [-1 0] are interpreted as node negative tumours and [0 1] as node positive ones. The network outputs are then compared with the desired target values and the network’s performance is obtained in terms of the percentage of the test samples classified correctly; this is referred to as network’s accuracy.

Table I. Markers recorded for breast cancer patients.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Attributes</th>
<th>No. of available cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour Size</td>
<td>0.4-8</td>
<td>102</td>
</tr>
<tr>
<td>Ki-67</td>
<td>0.1-0.73</td>
<td>73</td>
</tr>
<tr>
<td>ER (Oestrogen Receptor Status)</td>
<td>-1, 1</td>
<td>106</td>
</tr>
<tr>
<td>PR (Progesterone Receptor Status)</td>
<td>-1, 1</td>
<td>106</td>
</tr>
<tr>
<td>P53</td>
<td>0-0.9</td>
<td>72</td>
</tr>
</tbody>
</table>

PNN. Probabilistic neural networks (PNN) are a class of Bayesian neural networks which are employed to classify different output patterns based on a set of input data (24, 25). A PNN, for which a two-class output structure is illustrated in Figure 2, is composed of four layers: the input, pattern, summation and the output layer.

During the training mode, the weights between the input and pattern layers \( w_{ip} \) are set equal to those of the training samples \( x_{ip} \) which are presented at the input layer. Therefore, the sizes of input and pattern layers are determined by the input vector’s dimension \( n \) and the number of training patterns \( P \) respectively, where the number of training patterns \( P \) is the sum of the patterns in two groups \( p_1 \) and \( p_2 \). The size of summation layer is determined by the number of groups to be classified. Hence, in the present application the summation layer consists of two units for which the weights \( w_{jp} \) are adjusted to 1 if the training pattern belongs to the class associated with that unit and is 0 otherwise.

The PNN classifies each new pattern as a member of one of the two or more output classes by modelling a Bayesian classifier. This is carried out by estimating the probability densities of the training
patterns to be separated using Parzen-Window density estimation, in which pdf of a set of given patterns is estimated in a non-parametric manner by superimposing a set of window functions (kernels) placed on each pattern (26). Therefore, assuming two groups of data to be classified including \( p_1 \) and \( p_2 \) number of patterns (represented as \( p_j \) with \( j = 1, 2 \)), the pdf of each group \( f_j(X) \) can be estimated as:

\[
f_j(X) = \frac{1}{p_j n^s} \sum_{p=1}^{p_j} \sum_{i=1}^{n} k \left( \frac{x_i - x_{ip}}{s} \right)
\]  

(Equation 5)

where \( X \) is the input vector to be classified and \( x_{ip} \) is the \( p^{th} \) training pattern, the index \( i \) refers to each member of the input vector which are \( n \) in total and specify the input vector dimension. The width of the window is specified by \( s \) which is the smoothing parameter. A multivariate Gaussian kernel is commonly used in a Parzen-Window pdf estimator and hence \( f_j(X) \) can be represented as:

\[
f_j(X) = \frac{1}{(2\pi)^{p/2} s^p} \sum_{p=1}^{p_j} \sum_{i=1}^{n} \exp \left( \frac{\|x_i - x_{ip}\|^2}{2s^2} \right)
\]  

(Equation 6)

In the PNN, classification is carried out by estimating the \( f_j(X) \) for each output class and assigning \( X \) to the class which obtains the highest value. In Equation 6, \( s \) is the width of the Gaussian function called ‘spread’ in the PNN. The value of spread signifies the amount of separation of the input patterns and is usually defined by trial and error and based on the given data. In effect, pattern and summation layers of a PNN form a Parzen-window pdf estimator in which a set of Gaussian windows centred at each training pattern are usually used as the kernel parameter.

The network’s outcome, which is provided by the output layer is either 1 for patients without any positive nodes or 2 for the patients with at least one positive node. To evaluate the accuracy of the PNN’s outcome for prediction of nodal involvement, the data set is divided into the training and test parts.

The train/test set selection is also an important issue in neural networks. Random selection of the sets is commonly used in ANN applications. However, a drawback is that the results are slightly different in each run due to the random selection of the sets. Hence, we have used a more reliable method for splitting the set called the leave-one-out method (LOO). In this method, all the data records except one, which is reserved for the test, are used for training the network. This process is replicated until all the records in the data are used once for the test. Afterwards, the final output accuracy is computed by averaging the output accuracies obtained from each test data. The results presented in the next part are obtained from the test set. MATLAB was used for the simulations.

Results

The prediction results obtained by the analysis of 5 markers and all of their 31 possible combinations by means of the MLP and the PNN are tabulated in Tables II and III. Each combination is defined by a “Group No.” and some asterisks (\(^\#\)) showing the relevant group’s marker(s). In this table, PPV and NPV stand for positive and negative predictive values, presented in percentage, respectively.

PPV and NPV were calculated using true positive (TP), true negative (TN), false positive (FP) and false negative (FN) values to simplify the results’ interpretation. TP, TN, FP and FN stand for: a) TN: the percentage of node-positive samples classified as node-positive; b) TP: the percentage of node-negative normal samples classified node-negative; c) FP: the percentage of node-positive classified as node-negative; and d) FN: the percentage of node-negative samples classified as node-positive.

PPV value indicates the network’s ability to correctly predict node positive tumours and is defined as:

\[
PPV = \frac{TP}{TP + FP}
\]  

(Equation 7)
NPV specifies the network’s ability in correctly predict normal cases and is calculated as:

\[ NPV = \frac{TN}{TN+FN} \]  
(Equation 8)

Sensitivity value indicates the network ability in correctly predicting normal cases and is defined as:

\[ Sensitivity = \frac{TP}{TP+FN} \]  
(Equation 9)

Specificity specifies the network ability in correctly predicting cancer cases and is calculated as:

\[ Specificity = \frac{TN}{TN+FP} \]  
(Equation 10)

The best result was obtained with the combination including ER and p53 with 62.1% accuracy. This combination maintained the highest PPV of 67%, a good NPV of 55%, a good sensitivity of 54% and the highest specificity of 69%. The results obtained by the PNN using all marker combinations are given in Table III.

As stated before, the network’s performance in terms of success in arriving at a correct prediction would be evaluated and regarded as the network’s accuracy.

The results obtained by the MLP using all marker combinations are tabulated in Table II. The first row displays all the markers employed for outcome prediction while in the subsequent rows different subsets’ marker elements are indicated by “★” symbol.

In the PNN, the best accuracy was obtained by group 13 including tumour size, PR and p53 which provided the best overall results obtaining the highest test accuracy and a high value for all measured variables including PPV, NPV, sensitivity and specificity. Therefore, it can be deduced that this group is of high prognostic significance for predicting both node-negative and node-positive occurrences.
PR individually provided 100% specificity which can be explained by the high prognostic value of PR in lymph node-negative tumours. However, the sensitivity value provided by this marker was low at 0 which makes the use of PR implausible as a single marker for the prediction of nodal status.

The results of LOO method show little variation comparing to the full marker set except for leaving out the tumour size which led to a considerable decline in test accuracy. Inspecting for other measured variables, we may infer that this decrease is mainly due to lower node the -negative prediction as the specificity value had dropped significantly in the absence of tumour size. Therefore, it appears that tumour size plays an important role in node-negative tumours.

It is noteworthy that the group including all markers and that including all markers except Ki-67 provide exactly the same predictive results. While these two groups result in a good PPV, NPV, specificity and overall test result, the obtained sensitivity is low. We infer that although Ki-67 is associated with tumour aggressiveness and progression and is considered as an important prognostic marker for survival prediction by several studies (12, 13, 30), it is not an effective prognostic marker for the prediction of nodal status, neither individually nor in combination with other markers.

Tumour size appears to be the most important individual marker as it predicts nodal status with 61% accuracy alone and provides a good result for PPV, NPV and specificity. However, employing this marker alone for prediction of nodal status is not recommended as the provided sensitivity value is below 50%.

Discussion

The relative merits of the analytical systems employed here may be summarised as a prelude to the discussion of the outcome of the analyses. The PNN maintains some unique advantages which makes it an alternative ANN structure to the MLP for some classification problems. These advantages include its rapid training – it is many times faster than the BP...
algorithm and guaranteed convergence to the optimal Bayes classifier. It is easily modified by adding new training data and hence is compatible with online applications, unlike the BP algorithm which needs to be re-trained for any modification in the training data. Furthermore, the PNN outputs are interpretable in the sense that the inputs can be characterized by the amount of their effectiveness in making the output decision (29). On the other hand, the PNN requires a large amount of memory to run, as all the training data needs to be stored during the PNN training process (25). However, this is not a huge disadvantage as the number of available data in medical applications and especially, in the domain of cancer are always limited and hence the amount of required memory to store the data does not pose a problem.

In the present study, our main purpose was to evaluate five tumour biomarkers for their predictive significance associated with metastasis to axillary lymph nodes. These markers included tumour size together with four biomolecular markers, ER, PR, and p53, Ki-67 expression. The assessment of these markers was carried out using an MLP and a PNN. A further objective of the study was to analyze the interactions between individual markers and how they affect predictive outcome.

By comparing the network outcome for different marker groups, we observed that the best prediction was obtained from the combination of tumour size, PR and p53, with 71% test accuracy while this group maintained the highest NPV at the same time. Moreover, this subset gave a sound value for sensitivity which is considerably low in other combinations.

The results indicate that including tumour size in different combinations results in a significant increase in the predictive score which proves the predictive value of tumour size in prediction of cancer prognosis. This can also be explained by the higher invasive ability of larger tumours.

The predictive significance of steroid receptor status, as an independent marker of cancer progression and prognosis, has often been the focus of debate. The results of the present study indicate that omitting one of the steroid receptors from the markers does not affect the output accuracy significantly. This can verify the interaction between signaling by the steroid hormones through their respective receptors. However, the exclusion of both ER and PR from the markers results in a considerable reduction in the predictive ability of the group. Hence, we may conclude that ER/PR might influence prediction as independent factors although the presence of either would suffice to provide the biological factor required for asserting predictive ability.

The significant reduction of prediction accuracy in the absence of both ER and PR might also be considered as an indication of compensative role of these receptors for the omission of p53/Ki-67. Furthermore, the slight loss in predictive accuracy resulting from the omission of p53 expression suggests that p53 might not be an independent marker of progression.

Excluding Ki-67 resulted in a slight increase in the output accuracy. Including the Ki-67 in different combinations however, did not remarkably reduce the predictive outcome. This might suggest that this marker offers similar information for node-positive and node-negative tumours and confirms the results obtained Van Oijen et al. regarding the presence of Ki-67 expression in non-proliferating cells as well as proliferating ones (15).

In conclusion, the present study proposes specific combinations of this panel of markers as possessing a significant predictive value in breast cancer. High output accuracy has been obtained here by markers in specific combinations and this emphasizes the need to test and employ tumour markers in combinations in order to reduce the application of invasive procedures and in this way reduce morbidity in patients and lead to a vital reduction in the cost of patient management.

References


Received July 5, 2013
Revised July 22, 2013
Accepted July 23, 2013