Journal of Cytology & Histology
ISSN: 2157-7099

Ajili et al., J Cytol Histol 2014, 5:3
DOI: 10.4172/2157-7099.1000226

Research Article Open Access

# Prognostic Value of Artificial Neural Network in Predicting Bladder Cancer Recurrence after BCG Immunotherapy

**Faouzia Ajili[1]*, Ben Mhamed Issam[2], Saber Abid[2], Amine Darouiche[3], Mohamed Chebil[3], Samir Boubaker[1]**

[1]*Laboratory of Human and Experimental Pathology, Pasteur Institue of Tunis, Tunisia*
[2]*Higher School of Sciences and Techniques of Tunis,University of Tunis, Tunisia, Signal, Image and Intelligent Control of Industrial Systems*
[3]*Department of Urology, Charles Nicole Hospital, Tunis, Tunisia*

## Abstract

**Background:** Artificial neural network (ANN) has been used in medicine to predict either the treatment or the investigative outcomes. The aim of this study was to validate the use of ANN models for predicting recurrence in non muscle invasive bladder cancer (NMIBC) treated by Bacillus Calmette Guerin (BCG) immunotherapy.

**Materials and Methods:** In this study, we developed a Multilayer Percepteron (MLP) based ANN to detect recurrence in NMIBC through the analysis of histopathologic data. The study includes 308 patients (mean age, 63.92 years; range, 31-92 years) who were treated with transurethral resection followed by BCG-immunotherapy. Time follow-up was 30 months.

**Results:** In the test group, 39 out of 40 cases were correctly classified by the MLP base neural network with an optimum Mse error (0.02634). Only one case was classified as false positive, with no false negative results. The sensitivity, specificity, positive predictive and negative predictive values calculated from the output data were 96.66%, 100%, 100% and 90.9% respectively. Network can predict the outcome of 79% (34*100/35) of patients in the testing data set correctly.

**Conclusion:** The proposed algorithm produced high sensitivity and specificity in predicting the recurrence in NMIBC after BCG immunotherapy compared to conventional statistical analysis. Therefore the use of ANNs will increasingly become the method of choice to calibrate complex medical models.

**Keywords**: Bladder cancer; BCG-immunotherapy; Prognostic; Artificial neural network; Recurrence

## Introduction

Non-muscle-invasive bladder cancer (NMIBC) is a slow-growing tumor which recur in 48% to 70% of cases after transurethral bladder tumor resections, and 10% to 48% of these recurrent tumors have the potential to became muscle invasive and metastatic [1-3]. Until now, intravesical bacillus Calmette-Guerin (BCG) instillations have proven to be the most successful adjuvant treatment for patients with intermediate- and high-risk non–muscle-invasive bladder cancer. However, no markers are available to predict BCG immunotherapy response. For those reasons, many studies have been conducted to develop scales to predict the recurrence and progression of these tumors [4-9].

Predictive models are used in a variety of medical domains for diagnostic and prognostic tasks. These models are built from experience, which constitutes data acquired from actual cases. Data can be pre-processed and expressed in a set of rules, such as training data for statistical and medical learning models. Among the options in the latter category, the most popular models in medicine are logistic regression (LR) and artificial neural networks (ANN) which is an artificial intelligence tool that identifies arbitrary nonlinear multiparametric discriminant functions directly using clinical data. ANNs are non-linear mapping structures based on the function modeling of the human brain. They are powerful tools for modeling. It can identify and learn correlated patterns between input data sets and corresponding target values. After training, ANNs can be used to predict the outcome of new independent input data. On the other hand, ANNs imitate the learning process of the human brain and can process problems involving non-linear and complex data even if the data are imprecise and noisy. The use of ANNs has gained increasing popularity for applications where description of the dependency between dependent and independent variables is either unknown or very complex. This learning technique can be roughly described as a universal algebraic function that will distinguish signal from noise directly using clinical data. The application of ANNs to complex relationships makes them highly attractive for the study of complex medical decision making. The MLPs are the most commonly used model from the several kinds of ANN. They are known by learning and generalization and classification capacities. In medicine, MLP has been used to predict either the treatment or the investigative outcomes. In this study, we investigated the use of MLP to predict the early recurrence of non muscle invasive bladder cancer. This will serve as a predictive tool in determining the most appropriate adjuvant treatment after transurethralresection (TUR) and to prevent recurrence and progression.

***Corresponding author:** Ajili Faouzia, Laboratory of Human and Experimental Pathology, Pasteur Institute of Tunis, Tunisia, Institut Pasteur de Tunis, 13, Place Pasteur, 1002 Tunis, Tunisia, Tel: 00 21671789 608; Fax: 00 21671791 833; E-mail: Faouziaagili@yahoo.fr

**Received** February 17, 2014; **Accepted** March 10, 2014; **Published** March 12, 2014

**Citation:** Ajili F, Issam BM, Kourda N, Darouiche A, Chebil M, et al. (2014) Prognostic Value of Artificial Neural Network in Predicting Bladder Cancer Recurrence after BCG Immunotherapy. J Cytol Histol 5: 226. doi:10.4172/2157-7099.1000226

## Patients and Methods

### Patients

During an 8-year period from 2002 to 2010, a total of 308 consecutive patients with histopathologically confirmed NMIBC including pTa and pT1 stages with or without concomitant CIS, were recruited from the Department of urology of Charles Nicole Hospital, Tunisia. All the tumours were totally removed endoscopically. All the patients had received six weekly instillations of BCG (BCG Pasteur strain, 75 mg in 50 ml saline), three to six weeks after the last transurethral resection. After the last instillation, urine cytology and cystoscopic examination were performed. If these examinations were negative, patients continue the treatment of maintenance which consists in 24 additional monthly instillations. The follow up was performed for 30 months. The resulting gradewas evaluated according to the 2004 WHO grading system [10]. The most widely used and universally accepted staging system is the tumour-node-metastases (TNM) system [11]. All patients were informed about the aim of the study and signed a written consent stating their agreement to participate in the trial. Information was obtained on professional data. For each patient, data were collected on multiplicity (single or multiple), histological grade (high grade or low grade) and stage (pTa or pT1). Patients underwent urine cytology and cystoscopy every 3 months for 2 years during treatment and every 6 months thereafter. Responders to BCG-immunotherapy were defined as patients who did not show cystoscopic or cytological evidence for tumour recurrence during the follow-up. Recurrence was defined as reappearance of tumour after the initial treatment with at least one tumour-free cystoscopy interval. All patients were informed about the aim of the study and signed a written consent stating their agreement to participate in the trial. The present study was also approved by the local research ethical committee of the Pasteur Institute of Tunis which is in agreement with Helsinki declaration. The end-point for follow-up was either development of recurrence or thetermination date of the study.

### Methods

In this study, an MLP was implemented in the MATLAB software package (MATLAB version 6.5 with neural network toolbox), with the error back propagation algorithm used in the learning phase.

The general scheme of an MLP is shown in Figure 1. Each layer is composed of a pre-defined number of neurons. It has one or more HLs with a linear combination function is the inner product of inputs, weights and a bias. Activation function is *logistic* or *tanh* function. Inputs were fully connected to the first HL, each HL is fully connected to the next, and the last HL is fully connected to the outputs. MLPs use supervised learning or back propagation.

The used MLP consists of three layers: an input layer, an output layer, and one or more hidden layers (HL).

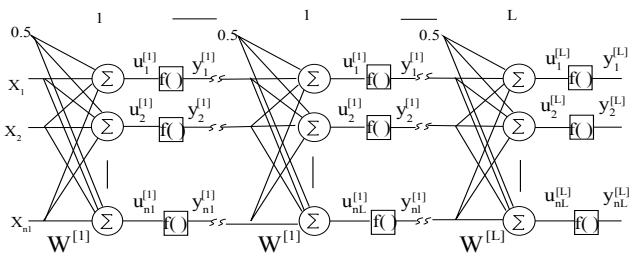


**Figure 1:** Fully connected feed forward multilayer perceptron.

Designing and training an MLP requires:

i) Selecting number of HLs.

ii) Number of neurons to be used in each HL.

iii) Avoiding local minima.

iv) Converging to an optimal solution in a reasonable period of time.

v) Validating NN to test for over fitting.

MLPs are used in classification problems, in fitness approximations [12-16].

Age, gender, tumour stage and grade, carcinoma in situ, tumour size, multiplicity, smoking and CD34 expression were used as input data for the ANN. Time to event and censoring information were not used by the neural network. Target variables were tumour recurrence. For each endpoint, 500 different ANN were constructed using the three-layer feed-forward multilayer perceptron architecture. This is the most common ANN type, which consists of an input layer, a hidden layer, and the output neuron. Each input neuron (perceptron) receives data from one input variable. 70% of the cases (patients) wereselected by random and used for the training process, and the remaining 30% served as independent validation data set. This random split was repeated for every new ANN model. During training, the network calculates a decision (classification) for each case of the training data set. Then, the prediction is compared with the true category of each case, and the classification error is calculated. In order to minimize the error, the neurons and interconnections ("weights") of the ANN are adjusted, and the next training cycle begins. This iterative training process is repeated until the classification error reaches a minimum. After training is finished, the network is tested by using the validation data set.

## Results

In this study, data from 268 from 308 subjects were used for training, and the rest of them were used for control and testing procedures. Indeed, to test the Neural Network performance after the training step one needs several known patterns used as benchmarks. For this purpose the common used approach is to divide the dataset into two parts. The first part is used for training and the second is used for testing (usually 10% of the dataset is used for testing). In our application we have 307 patients then we use 268 for training and 39 patients (about 12% of the total dataset) for training.

To reduce network training epoch number and to obtain a better network result or generalization data, all of data were simply pre-classified with respect to patient age, gender, smoking, tumor stage, tumor grade, tumor size, carcinoma in situ, multiplicity and CD34 expression. The network outputs represented by unit basis are as follows:

1: No recurrence (response to BCG immunotherapy)

0: Recurrence (No response to BCG immunotherapy)

The trained networks have 7 input units, one hidden layer with 20 units and 1 output neuron as shown in Table 1. In order to make this classification, four-layered perceptron was employed and trained by the back propagation learning algorithm. The sigmoid function $f(x)=\frac{1-e^{-\lambda}}{1+e^{-\lambda}}$ was selected as the transfer function that is used to determine theoutputs according to the neuron inputs.

The testing mean square error (MSE) was obtained 0.02634 from

| Architecture | Training/Testing parameters | | | |
|---|---|---|---|---|
| **The number of layers** | **3** | **Training algorithm** | | **Back propagation algorithm** |
| The number of processing elements on the layers | Input | 7 | Mean square error (mse) | Training 0.0001 |
| | Hidden | 12 | | Testing 0.02634 |
| | Output | 1 | | 1000 |
| Activation function | Sigmoid function | | Epoch number | |

**Table 1:** Artificial neural network architecture and training/testing parameters.

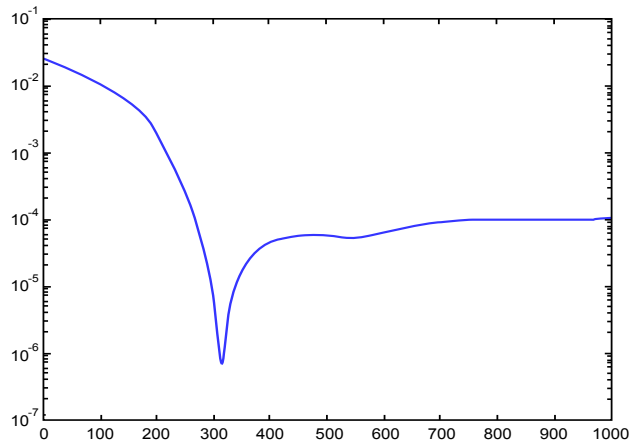


**Figure 2:** The error variations with respect to training epoch numbers (sum squared error, Mse, was selected 0.0001. If Mse value is equal to 0.0001, training iterations is stopped).

| Output name | *n* | Recognition rates | |
|---|---|---|---|
| | | True | False |
| Positive (response to BCG) | 30 | 29(96.66%) | 1(3.33%) |
| Negative (recurrence) | 10 | 10(100%) | 0(0%) |
| Total | 40 | 39(97.5%) | 1(2.5%) |

Sensitivity=TP/(TP+FN)=96.66%
Specificity=TN/(TN+FP)=100%
Positive predictive value=TP/(TP+FP)=100%
Negative predictive value =TN/(TN+FN)=90.9%
**Abbreviations:** TP: True positive; TN: True negative; FP: False positive; FN: False negative.

**Table 2:** The testing performance of the system based on artificial neural networks.

optimized multilayer perceptron feed forward network with training mean square error about 0.0001 at 1000 epochs.

After the training and testing procedures are completed, the results from the test data were analyzed in correlation with the histopathology results, which are considered as the golden standard in clinical decision making. For a practical applicability in the clinical decisions, the following statistical parameters were calculated:

Sensitivity=True positive/(True positive + False negative)

Specificity=True negative/(True negative+False positive)

Positive predictive value=True positive/(True positive + False positive)

Negative predictive value=True negative/(True negative+False negative)

## Training Neural Networks

In the test group, 39 out of 40 cases were correctly classified by the MLP base neural Network with an optimum Mse error (0.02634) (Figure 2). Only one case was classified as false positive, with no false negative results. The correlation between the ANN output and histopathology results are summarized in Table 2. The sensitivity, specificity,positive predictive and negative predictive values calculated from the output data were 96.66%, 100%, 100%, and 90.9%, respectively (Table 2). Network can predict the outcome of 79% (34*100/35) of patients in the testing data set correctly.

## Discussion

Tumor recurrence following transurethral resection (TUR) is a significant problem for both the patient and the clinician. Intravesical bacillus Calmette-Guerin (BCG) immunotherapy represents a highly successful therapy for patients with non–muscle-invasive bladder cancer (NMIBC) tumors [17-20]. These tumors show sometimes repeated superficial recurrences, but in some cases, they progresses into infiltrative or metastatic cancer despite diverse treatments. A significant portion of these patients fail to respond to BCG therapy; their tumours may became invasive or metastatic [19-22].

Artificial neural networks (ANNs) are now the most popular artificial learning tool in biotechnology. They have been used by various researchers to predict bladder cancer progression [23-25]. However, no study showed interest in predicting bladder cancer response to BCG immunotherapy. ANNs have an increasing popularity as a computational tool which is being evaluated in various medical areas including early detection, risk assessment, classification, and prognosis of disease states [26]. A significant advantage of this method is its ability to reveal complex relationships between available clinical data and the final outcome. In fact, ANN is a feasible and promising method to "learn" and handle the complex data patterns that occur in real clinical scenarios. This model can provide valuable assistance in decisions about the therapeutic strategy in daily practice, e.g. by using them in the clinic via a web interface. It has to be emphasized that decision supporting tools should serve as complementary tools in clinical decision making and should not be the sole base of clinical judgment. ANN provides risk assessment of each individual patient. Therefore, ANN can easily be used in urology to predict the response to BCG therapy and to help urologists in the planning of treatment.

In this study, we developed an MLP to detect recurrence after BCG immunotherapy in NMIBC through the analysis of histopathology data. To the best of our knowledge, our study is the first attempt to evaluate the role of ANN in predicting recurrence in NMIBC after BCG immunotherapy. Hereby, we found that the sensitivity, specificity, positive predictive and negative predictive values calculated from the output data were 96.66%, 100%, 100% and 90.9%, respectively. This shows that the proposed algorithm produced high sensitivity and specificity in predicting the histopathology results, showing that this method has a promising value in estimation of NMIBC recurrence.

On line with our work, many studies have shown a significant improved accuracy in diagnosing, staging and predicting post-treatment results for ANNs compared to conventional statistical analysis. Indeed, Qureshi et al. [27] evaluated the ability of an ANN to predict bladder cancer recurrence within 6 months of diagnosis and stage progression in patients with Ta/Tl bladder cancer. ANN predictions were compared withthose of four consultant urologists. The accuracy of the neural network in predicting stage progression and

recurrence within 6 months for Ta/T1 tumors and 32-month cancer-specific survival for T2–T4 cancers was 80%, 75% and 82%; respectively; with corresponding figures for clinicians being 74%, 79% and 65%. On the other hand Parekattil et al. [28] showed in a clinical trial on bladder cancer that ANNs model was more accurate in identifying patients who required cystoscopy, thereby providing possible savings. To summarize we can suggest that ANN models can be valuable tools in reducing the workload on the clinicians by detecting artifact and providing decision support. Therefore, the response to BCG therapy can be predicted, more accuracy than the current clinical methods, from a large group of patients compared to information of one given patient. After training, the networks could predict multiple patient outcomes from unrelated institutions.

Advantages of neural network analysis are that few prior assumptions or knowledge about data distributions are required, so knowledge about complex variable transformations is not needed before training, and the search for the optimal diagnostic classifier involves minimal user input. Another advantage is that ANN has the capacity to model complex nonlinear relationships between independent and predictor variables, allowing the inclusion of a large number of variables. Another significant advantage of this method is its ability to reveal complex relationships between available clinical data and the final outcome. Due to their multi-factor structure of medical problems, such relationships are difficult to be analyzed by conventional statistical methods [29,30]. Compared to the conventional statistical methods, they provide a superior accuracy [31,32]. Recent studies have demonstrated that neural network analysis is potentially more useful and superior than traditional statistical techniques when the importance of a given prognostic variable is expressed as a complex unknown function of the value of the variable or when the prognostic impact of a variable is influenced by other prognostic variables in a complex multidimensional nonlinear function [33-36]. Several disadvantage of ANN should be considered. First, the sample size was small. Second, thetraining process and requirement of an experienced operator is long to determine the optimal network topology. The major factor that needs to be experimentally determined is the number of hidden layer nodes. If too few hidden nodes are used, proper training is impeded. If too many are used, the neural network is over trained.

Apart from adding new potential variables, there are other features that can be regarded for future ANN model developments, such as using a larger number of patients and collecting data prospectively to avoid possible bias in patients and treatment characteristics. In addition, the performance of ANN could be further improved by including new cases from other centers due to the unique ability of learning of neural networks.

## Conclusion

The proposed algorithm produced high sensitivity and specificity in predicting the recurrence in NMIBC after BCG immunotherapy compared to conventional statistical analysis. Therefore the use of MLP will increasingly become the method of choice to calibrate complex medical models. Indeed, MLP will allow a patient-oriented individualdecision tool, relying on a waste base of information and decisions. They are able to combine biochemical markers, imaging studies and other tools with personal experience and act as a thinking module. However, prospective validation using a standardized multi-institutional database to overcome the pitfalls of MLP is required.

### References

1. Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, et al. (2006) Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. EurUrol 49: 466-477.
2. Oosterlinck W, Lobel B, Jakse G, Malmström PU, Stöckle M, et al. (2002) Guidelines on bladder cancer. EurUrol 41: 105-112.
3. Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Algaba F, et al. (2000) Primary superficial bladder cancer risk groups according to progression, mortality and recurrence. J Urol 164: 680-684.
4. Kurth KH, Denis L, Bouffioux C, Sylvester R, Debruyne FM, et al. (1995) Factors affecting recurrence and progression in superficial bladder tumours. Eur J Cancer 31A: 1840-1846.
5. Millán-Rodríguez F, Chéchile-Toniolo G, Salvador-Bayarri J, Palou J, Vicente-Rodríguez J (2000) Multivariate analysis of the prognostic factors of primary superficial bladder cancer. J Urol 163: 73-78.
6. Solsona E, Iborral, Dumont R, Rubio-Briones J, Casanova J, et al. (2000) The 3-month clinical response to intravesical therapy as a predictive factor for progression in patients with high risk superficial bladder cancer. J Urol 164: 685-689.
7. Kaasinen E, Rintala E, Hellström P, Viitanen J, Juusela H, et al. (2002) Factors explaining recurrence in patients undergoing chemoimmunotherapy regimens for frequently recurring superficial bladder carcinoma. EurUrol 42: 167-174.
8. Kwak C, Ku JH, Park JY, Lee E, Lee SE, et al. (2004) Initial tumor stage and grade as a predictive factor for recurrence in patients with stage T1 grade 3 bladder cancer. J Urol 171: 149-152.
9. Choi CK, Kim JS, Rim JS (1999) Application of scoring system reflecting various prognostic factors to the prediction of recurrence in superficial bladder carcinoma. Korean J Urol40:878-885.
10. Sauter G, Algaba F, Amin MB (2004) Non invasiveurothelialtumors, In: Elbe JN, Sauter G, Epstein JI, SesterhennIA, Pathology and Genetics. Tumors of the Urinary System and Male Genita Organs. IARC Press, Lyon.
11. Sobin DH, Wittekind CH (2002)_TNM classification of malignant tumours, (6thedn), Wiley-LissNew York.
12. Cybenko G (1989) Approximation by superpositions of a sigmoidal function. Math. Contr. Signals Syst 2: 303-314.
13. Devijver PA, Kittler J (1982) Pattern Recognition: A Statistical Approach. Englewood Cliffs, NJ: Prentice-Hall, 1982.
14. Hornik K (1989) "Multilayer feedforward networks are universal approximators," Neural Networks 2: 359-366.
15. Judd JS (1990) Neural Network Design and the Complexity of Learning, Cambridge, MA: The MIT Press.
16. Hagan TM, Demuth HB, Beale M (1996) Neural Network Design. Cengage Learning India.
17. Morales A, Eidinger D, Bruce AW (1976) Intracavitary Bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol 116: 180-183.
18. Lamm DL (2000) Preventing progression and improving survival with BCG maintenance. EurUrol 37 Suppl 1: 9-15.
19. Patard JJ, Rodriguez A, Leray E, Rioux-Leclercq N, Guillé F, et al. (2002) Intravesical Bacillus Calmette-Guerin treatment improves patient survival in T1G3 bladder tumours. EurUrol 41: 635-641.
20. Saint F, Salomon L, Quintela R, Cicco A, Hoznek A, et al. (2003) Do prognostic parameters of remission versus relapse after Bacillus Calmette-Guérin (BCG) immunotherapy exist?.analysis of a quarter century of literature. EurUrol 43: 351-360.
21. Sylvester RJ, van der Meijden APM, Oosterlinck W, Witjes JA, Bouffioux C, et al. (2006) Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 49: 466-477.
22. Fernandez-Gomez J, Solsona E, Unda M, Martinez-Piñeiro L, Gonzalez M, et al. (2008) Prognostic factors in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guerin: multivariate analysis of data from four randomized CUETO trials. Eur Urol 53: 992-1002.

23. Abbod MF, Linkens DA, Catto JW, Hamdy FC (2006) Comparative study of intelligent models for the prediction of bladder cancer progression. Oncol Rep 15 Spec no.

24. Catto JW, Linkens DA, Abbod MF, Chen M, Burton JL, et al. (2003) Artificial intelligence in predicting bladder cancer outcome: a comparison of neuro-fuzzy modeling and artificial neural networks. Clin Cancer Res 9: 4172-4177.

25. Fujikawa K, Matsui Y, Kobayashi T, Miura K, Oka H, et al. (2003) Predicting disease outcome of non-invasive transitional cell carcinoma of the urinary bladder using an artificial neural network model: results of patient follow-up for 15 years or longer. Int J Urol 10: 149-152.

26. Kapetanovic IM, Rosenfeld S, Izmirlian G (2004) Overview of commonly used bioinformatics methods and their applications. Ann N Y AcadSci 1020: 10-21.

27. Qureshi KN, Naguib RN, Hamdy FC, Neal DE, Mellon JK (2000) Neural network analysis of clinicopathological and molecular markers in bladder cancer. J Urol 163: 630-633.

28. Parekattil SJ, Fisher HA, Kogan BA (2003)Neural network using combined urine nuclear matrix protein-22, monocyte chemoattractant protein-1 and urinary intercellular adhesion molecule-1 to detect bladder cancer. J Urol 169: 917-920.

29. Lisboa PJG, Ifeachor EC, Szczepaniak PS (2000) Artificial neural networks in biomedicine. London: Springer-Verlag.

30. Long WJ (2001) Medical informatics: reasoning methods. ArtifIntell Med 23: 71-87.

31. Abbod MF, Linkens DA, Catto JW, Hamdy FC (2006) Comparative study of intelligent models for the prediction of bladder cancer progression. Oncol Rep 15: 1019-1022.

32. Catto JW, Linkens DA, Abbod MF, Chen M, Burton JL, et al. (2003). Artificial intelligence in predicting bladder cancer outcome: a comparison of neuro-fuzzy modeling and artificial neural networks. Clin Cancer Res 9: 4172-4177.

33. Cross SS, Harrison RF, Kennedy RL (1995) Introduction to neural networks. Lancet 346: 1075-1079.

34. Baxt WG (1995) Application of artificial neural network to clinical medicine. Lancet 346: 1135-1138.

35. Cucchetti A, Vivarelli M, Heaton ND, Phillips S, Piscaglia F, et al. (2007) Artificial neural network is superior to MELD in predicting mortality of patients with end-stage liver disease. Gut 56: 253-258.

36. Piscaglia F, Cucchetti A, Benlloch S, Vivarelli M, Berenguer J, et al. (2006) Prediction of significant fibrosis in hepatitis C virus infected liver transplant recipients by artificial neural network analysis of clinical factors. Eur J Gastroenterol Hepatol 18: 1255-1261.