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Review

Artificial Neural Networks for Decision-Making in Urologic Oncology

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Abstract

The authors are presenting a thorough introduction in Artificial Neural Networks (ANNs) and their contribution to modern Urologic Oncology.

The article covers a description of Artificial Neural Network methodology and points out the differences of Artificial Intelligence to traditional statistic models in terms of serving patients and clinicians, in a different way than current statistical analysis.

Since Artificial Intelligence is not yet fully understood by many practicing clinicians, the authors have reviewed a careful selection of articles in order to explore the clinical benefit of Artificial Intelligence applications in modern Urology questions and decision-making.

The data are from real patients and reflect attempts to achieve more accurate diagnosis and prognosis, especially in prostate cancer that stands as a good example of difficult decision-making in everyday practice.

Experience from current use of Artificial Intelligence is also being discussed, and the authors address future developments as well as potential problems such as medical record quality, precautions in using ANNs or resistance to system use, in an attempt to point out future demands and the need for common standards.

The authors conclude that both methods should continue to be used in a complementary manner. ANNs still do not prove always better as to replace standard statistical analysis as the method of choice in interpreting medical data.

Keywords: Artificial Neural Networks; ANN; Urology; Prostate cancer; Diagnosis; Staging; Prognosis; Treatment; Recurrence

1. What is an Artificial Neural Network and how does it work?

Artificial Intelligence is not a new issue. Artificial Neural Networks (ANNs) have been a field of research for over the past 40 years [1]. The first computational, trainable neural networks were developed in 1959, by Rosenblatt [2] as well as by Widrow and Hoff [3] and Widrow and Stearns [4]. The first ANNs were perceptrons limited in a solution of simple linear problems. The first non-linear capabilities of ANNs were reported in 1974 by Werbos [5].

Artificial Neural Networks are computational methodologies that perform multifactorial analyses, inspired by networks of biological neurons. In biology, nervous networks are composed by a large number of neuron cells that are extensively interconnected to each other. Each neuron cell can produce an electrochemical signal. Through a complicated web of branches, known as dendrites, it can also interact with other neurons that may be closer or distant to it. Also there exists a network of output branching structure, known as axons, that is used for carrying out a certain message (signal). The interactions between axons and dendrites of neighboring or distant neurons, through synapses, help as to the interpretation of a signal. Moreover, the coming of a signal results to a response and careful regulation of its

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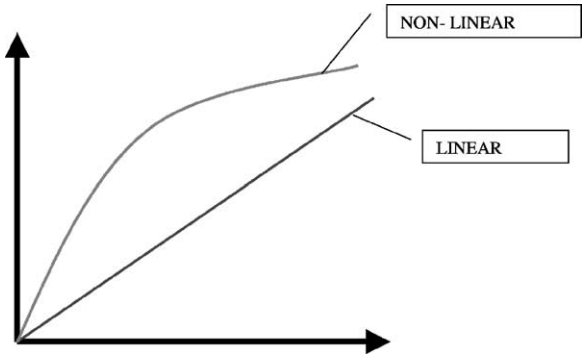

Fig. 1. Examples of two simple relationships between hypothetical parameters.

transfer by the synapses, something that is thought to be the primary event for learning.

As a neural network, Artificial Neural Networks also contain layers of simple points (nodes) of data, that interact through carefully weighted connection lines, so that they may process an outcome (Fig. 1). The weight-balance of these lines is accomplished by a training session of input data, to be used by the network as the means for the adjustment of its interconnections (learning or training session). Of course, current ANNs have a much simpler architecture, with a lot fewer nodes or interconnections than the actual nervous system (Fig. 2).

In order to understand the function of an Artificial Neural Network, one should rethink decision-making in oncology. Oncologic decision-making is based on a learning part and then it produces an outcome. The learning part of our decision-making consists from the collection of data that is interpreted and by so weighted from our medical knowledge and experience. By this means, our practice is carefully 'trained' for a decision analysis, in order to produce an outcome.

Upon dealing with a new patient, we tend to collect pure data (i.e. performance status evaluation, useful blood serum values, physical examination remarks, and imaging or histology details), in order to assess his situation and predict a prognosis and then proceed on making a decision based on our medical knowledge and experience. A clinician shall decide upon his perceptive of the disease progress but also carefully weight his decision by the individual's pattern recognition.

Likewise, in ANNs, there is a "learning" session. It is important to note that when training a neural network, three non-overlapping sets of data must be used. Typically data from a single population is divided at random, into three subsets: the training set, the validation (or testing) set and the verification set [1]. The training set is used as input signals of data to be fed to one or more layers of neurons through the weighted interactions between them and adjust their weights. The training process is accomplished by a teaching program that picks cases from a database in order to adjust the interactions between the layers as to produce an outcome that is close to the real world results from the same database. The training process keeps on as to minimize the error possibility, as for the ANN to 'learn' and produce an outcome similar or closer to the database's known or desired output values, and it stops up to where there is no indication of further diminishing of this error possibility (validation). The testing or validation set of data is therefore used to decide when

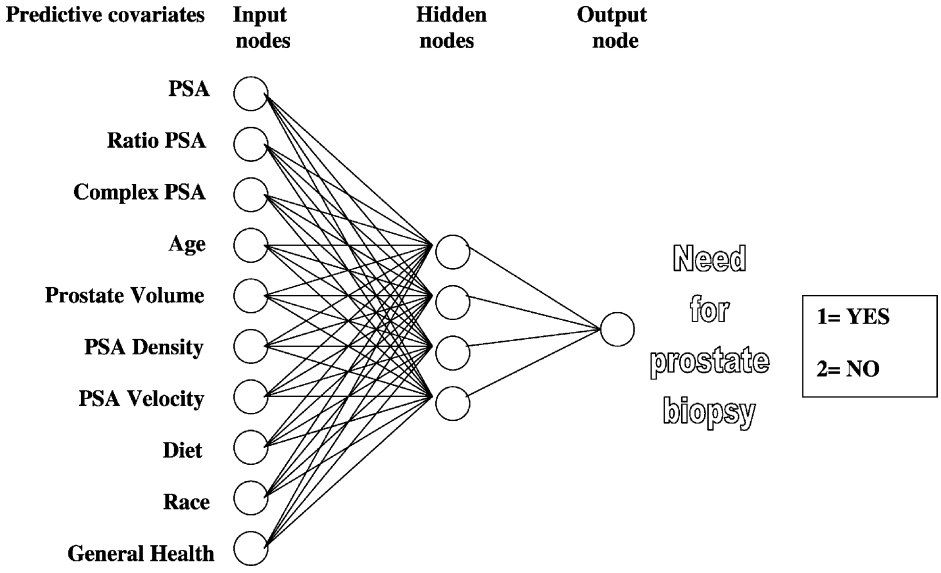

Fig. 2. Example of a neural network's interconnections (prostate cancer biopsy).

to stop training. By this accomplishment of minimum error, an ANN avoids over training. An example of this type of error is the failure to generalize, e.g. failure to recognize similar patterns that do not present in the exact same way, and can be considered memorization of the data (memory effect). A third step is the verification process for which a third part of data is reserved (verification set). The verification set is independent and is not used at all during training or testing, thus it can be considered a true prediction of the neural network performance.

A successful training can result in interpretation of data by the ANN, in a mature and often original way. With the computing power of today's hardware, ANNs can easily handle non-linear phenomena of any type without requiring linear relationships that reflect simple correlations (e.g. a Prostate-Specific Antigen [PSA] rise should lead to a prostate biopsy).

So an ANN can correlate different predicting factors, find hidden interactions among variables, predict an outcome for a patient or groups, classify patients in risk groups, or approximate a function and complete a known pattern.

2. Applications in Medicine and Urology

Studies of prognostic factors in cancer have demonstrated that there is great need for accurate treatment and outcome prediction. The objectives of applying predictive factors to a model of statistical analysis are to give some indication on prognosis and aid the clinician in the planning of treatment. Especially in oncology, statistical models can serve as to stratify patients in risk groups, predict the stage of the disease, and foresee treatment outcome or recurrence probability.

The TNM system was the first attempt in this prediction. TNM is a classification system that describes the anatomic extent of cancer. It describes three different variables (Tumor Stage, Lymph Node Status, Distant Metastases) and by so it stratifies patients, predicts prognosis, foresees treatment outcome, etc. It has been serving clinicians for decades, and helps in the exchange of information and treatment planning. But it also has limitations as to its inability in incorporating many serum or pathologic factors that are of some importance for specific types of cancer.

Evidently, a growing need for a new predicting tool has emerged. This new tool must not have TNM's limitations, and also it must be swiftly adjustable in new modalities of data for a certain disease. Neural networks automatically allow (1) arbitrary non-linear relations between the independent and dependent variables and (2) all possible interactions between the dependent variables. Standard statistical approaches (e.g. logistic or Cox regression) require additional modeling to allow this flexibility [6].

Recent published data reports that neural networks can provide at least as accurate predictions as regression analyses, and usually they are performing significantly better, when compared by receiver operating characteristics (ROC), and areas under curve (AUC).

Although the use of ANNs in medicine is a rather recent phenomenon, there are many applications deployed as in the field of diagnosis, imaging, pharmacology, pathology and of course prognosis. ANNs have been used in the diagnosis of appendicitis, back pain, dementia, myocardial infraction, psychiatric disorders, acute pulmonary embolism, and temporal arteries [7].

In Urology, prostate cancer serves as a good example for the need for an ANN. Changes in terms of screening, the need for an early diagnosis, the need on tissue sampling and re-sampling from the organ are just a few key issues up to diagnosis. Moreover, if diagnosis of prostate cancer is finally established, then there is a need for staging, predicting outcome (prognosis), eliminating risk factors, making decisions concerning treatment and follow-up, and possibly dealing with the issue of a recurrence.

2.1. Prostate cancer early diagnosis and screening

Prostate-Specific Antigen is currently recognized worldwide for its clinical usefulness in early diagnosis of prostate cancer. There exists a substantial overlapping between PSA values from patients with prostate cancer and benign prostate hyperplasia or inflammation that is more critical in the so-called 'grey' area for PSA values of 4–10 ng/ml. The rate of incidence of prostatic cancer in men with a PSA value within this zone of PSA from 4 ng/ml to 10 ng/ml is approximately 22% on initial biopsy, while another 10% of cancers are to be discovered on repeat biopsy [8]. Various PSA-related parameters have been developed for optimizing the sensitivity and specificity of prostate cancer prediction in patients with PSA levels between 4 ng/ml and 10 ng/ml. These parameters include PSA density (PSAD), PSA-transition zone (PSA-TZ), PSA velocity (PSAV), age-adjusted PSA, and the percentage of free PSA to total PSA (PSA ratio). Although PSA ratio is recognized as the most useful method of improving Prostate Cancer Detection, this issue is a matter of serious debate [9–12].

We also used to consider a maximum normal PSA value of 4 ng/ml in order to make a first statement of a possible suspicion for the disease. Evidence has shown that approximately 30% of men undergo radical

prostatectomy and approximately 25% of men who are diagnosed with prostate cancer have a PSA value less than 4 ng/ml [13,14].

Similar rates of incidence of cancer are reported [14,16] in men whose PSA value is in the range from 2.5 ng/ml to 4 ng/ml, something that would increase the potential need for a biopsy in a lot of men that currently are being excluded.

A first remark would lead to the conclusion that the majority of men to undergo prostate biopsy will have a negative result for cancer, while the costs of these biopsies are huge.

Urologists should be able to identify those men with a higher probability of having prostate cancer and so exclude patients that are not likely to have cancer.

In this great dilemma in our practice, many clinical factors or serum PSA-related enhancements have been examined for their predictive accuracy. The use of Artificial Intelligence, in this particular field, has proved a better predictive performance for biopsy outcome, by combination of more than one of these predictive factors.

Babaian et al. [14] developed a neural network-derived algorithm based on retrospective data that studied 151 men with PSA values between 2.5 ng/ml and 4 ng/ml, who underwent an 11-core multisite directed biopsy. The ANN used variables such as age, total PSA, PAP, creatinine kinase and free PSA, while it consisted of three individually trained networks that were developed with data from retrospective studies coming from three institutions. Cancer was detected in 24.5% (37 of 151) of the patients. A comparison of the sensitivity, specificity and negative and positive predictive values between the neural network algorithm and the other PSA parameters showed that their Prostate Cancer Detection index (ANN-index) was significantly better in terms of specificity when sensitivity was constantly held at 92%. In terms of ROC-curve analysis, and area under curve though, the ANN-index did not outperform any other variable.

The authors concluded that there would be an important reduction of the costs from unnecessary biopsies to the health care system by an additional 39%, if their ANN-index is used instead of free/total PSA.

Published data by Djavan et al. [15] demonstrate the predictive accuracy of two different ANNs that were developed on the Vienna-based multicenter European referral database for the early detection of prostate cancer in men with total Prostate-Specific Antigen levels from 2.5–4 ng/ml to 4–10 ng/ml. In this article, ANNs are prospectively developed to predict the presence of prostate cancer and their predictive accuracy is compared with that obtained by conventional univariate statistical analysis of total PSA, ratio PSA, PSAD, PSA-TZ, total prostate volume, TZ volume and PSAV. The variables used by the ANN as more predictive (input variables) for total PSA levels (2.5–4 ng/ml) were in order of importance, PSA-TZ, PSA ratio, PSAD. The variables used by the ANN as more predictive (input variables) for total PSA levels (4–10 ng/ml) were in order of importance, PSA ratio, PSA-TZ, PSAV, free PSA, TZ volume, total PSA and PSAD.

The authors concluded that the predictive accuracy of both ANN models was superior to that of conventional PSA parameters, and resulted in fewer unnecessary biopsies although the difference between ANNs and Logistic Regression (LR) Analysis, was not always statistically significant.

Finne et al. [16] have reported a comparison of diagnostic performance in predicting biopsy outcome between a Multilayer Perceptron (MLP) and Logistic Regression (LR) Analysis, and univariate analysis regarding PSA ratio. Variables used in MLP model included total PSA, PSA ratio, prostate volume, DRE; while in LR, age and history of prostate cancer were also included. The author's statement was that in sensitivity given in the area 89–99%, the MLP had the better accuracy than the other two models of analysis, and the MLP model was more accurate than the LR model in higher sensitivity levels.

Systematic transrectal ultrasound guided biopsy is an accurate and safe procedure. But a serious decision-making issue is emerging, when a first set of biopsies is negative, and still the suspicion for prostate cancer remains. This fact can continue even after another set of biopsies or more. When do we stop this never-ending cascade? In recent studies, if prostate cancer is present, it was reported that the detection rate is 10–25% for a repeat biopsy [8,17].

Djavan and coworkers [18] have reported that ANNs can be of valuable outcome if they were used in this particular dilemma of modern Urology. They concluded that their ANN found a strong predictive pattern for the repeat biopsy outcome, by combining individual clinical and biochemical markers, and a specificity of 68% was achieved at high sensitivity levels.

Moreover, there are some reports about the use of ANNs in imaging protocols [35–37] that addressed the poor specificity of TRUS images in detecting prostate cancer, and also the fact of iso-echoic areas that may conceal cancer as well. The introduction of ANN in TRUS analysis of radical prostatectomy specimens demonstrated a significant enhancement in detecting prostate cancer. Although not all of the malignant samples were classified correctly (79% accuracy), all iso-echoic areas that hidden cancer were surprisingly

identified by the ANN [36]. Ronco and Fernadez [37] reported that an ANN that combined several clinical, biochemical and ultrasonographic variables achieved up to 81.82% of positive predictive value and up to 96.95% of negative predictive value versus 67.18% and 90.97%, respectively, when compared with those obtained with Logistic Regression, in predicting an outcome of cancer or not cancer, but ANN had 82% accuracy while LR performed 84%. Several similar reports [26–32,46] also present some promising data from the field of diagnosis in prostate cancer as well as it is resumed in Table 1.

2.2. Prostate cancer staging

Nomograms that were developed by Partin et al. [40] are currently the most widely used and accepted models for predicting pathological stage of the disease in cases of localized prostate cancer. These nomograms use the clinical stage, biopsy Gleason Sum and pretreatment PSA values in order to predict the likelihood of several pathological variables from the radical prostatectomy specimen (pathologic stage) in cases of localized cancer.

Murphy et al. [19] used staging predictive factors such as clinical state (remission or progression), recent TNM stage, bone scan and Prostascint scan together with serum PSA-related factors (PSMA, PSA, free PSA, complexed PSA, percent free PSA, percent complexed PSA) to study the staging abilities of an ANN. An ANN revealed that between the examined factors, PSA levels, bone scan and Prostascint scan were significant variables in predicting the nodal positive status with a higher specificity (near 50%) compared to traditional regression analysis (slightly above 20%). In a similar study by Batuello et al. [20], they used clinical stage, biopsy Gleason Sum and Prostate-Specific Antigen levels as input variables to feed an ANN, in order to predict lymph node (LN) spread. This is somewhat of the objective of Partin nomograms as well, yet in a selective area of LN metastasis. The aim of their ANN's approach was to identify the LN-positive individuals characteristics. Due to the fact that in their cohort of patients only 4.6% was actually LN positive, the ANN tried to recognize the characteristics of these individuals by classifying the patients as LN-negative, and so by trying to achieve a minimal error the training algorithm was prone to treat the scarce positive cases as 'noise'. By increasing the LN-positive cases empirically to 25%, the writers achieved a statistically important impact of LN-positive status in the weight-adjusted interconnections of their ANN. With the acceptance of their doing, they tried to simply point out the relationship between the output of the ANN and the prevalence of LN-positive cases.

By so, they also were able to interpret the risk of similar ANN score patients, in LN-positive status. And thus they made an individual risk of LN-positive status in patients with similar risks as the ANN calculated them.

Han et al. [21] used input variables that included preoperative clinical and pathologic parameters from patients after radical prostatectomy, in order to retrospectively feed an ANN, so that it would test their predictive value in staging the disease. The neural network that was used in this application was a Multilayer Perceptron (MLP) that typically has standard feed-forward topology and successive layers of adaptive weights. Overall, the ANN outperformed nomograms in predicting pathologic stage at the time of surgery and

Table 1
Published articles in the field of the use of ANNs in prostate cancer (reviews not included)

Reference	Application	Sensitivity (%)	Specificity (%)	Accuracy (%)
[14]	Diagnosis	92	62	
[15]	Diagnosis	95	59–67	0.87–0.91[a]
[16]	Diagnosis	90	46	56
[18]	Diagnosis	95	68	0.91[a]
[27]	Diagnosis			87
[28]	Diagnosis	90	97	
[29]	Diagnosis			0.95[a]
[30]	Diagnosis	81	92	90
[31]	Diagnosis			80
[32]	Diagnosis	72	78	77
[33]	Diagnosis	90	+32–44[b]	
[46]	Diagnosis	95	38	
[19]	Staging	95	48[c]	
[20]	Staging			0.81[a]
[21]	Staging			0.88[a]
[24]	Staging	79	81	
[34]	Staging	94	69	
[39]	Staging	81–100	72–75	
[35]	Imaging			87–99
[36]	Imaging	79		
[37]	Imaging			82
[22]	Prognosis			85
[23]	Prognosis	31	95[d]	
[24]	–//–			80
[25]	Prognosis			80
[26]	Prognosis	74	78	0.80[a]
[27]	Prognosis			90
[38]	Prognosis			80

[a] Area under ROC curve.
[b] This percentage shows the enhancement of ANN in terms of specificity, compared to PSA, percent free PSA specificity values.
[c] Refers as to nodal positivity, while traditional regression analysis is slightly above 20%.
[d] Refers as to prediction of five-year recurrence, while Logistics Regression using all input variables shows 16%.

was more accurate in terms of sensitivity and specificity and had a larger area under ROC curve than the Logistic Regression-based nomograms. It is far more important to outline that this study, that is including Alan Partin among its authors, admits that ANN served better than the Partin nomograms that are currently the golden standard for predicting the staging of the disease, although the authors admit that "... (they) did not applied the nomograms on an independent validation set because a significant portion of database was used to develop the regression analysis ...".

2.3. Prostate cancer progression

Prediction of biochemical failure after radical prostatectomy and the estimate for the need for adjuvant therapy by local irradiation, hormonal ablation or chemotherapy is still a matter of controversy. The overall rate of a positive surgical margin with radical prostatectomy is 28% [43,44]. In any case, the finding of a cancer-positive margin would suggest the failure in excision of all traces of local disease, and also the risk of biochemical and finally clinical progression. Serious decisions are to be made in a case that one should balance who would benefit the most of adjuvant therapy without taking unnecessary risks in terms of morbidity and mortality that come along the administration of such agents. An urologist must also take under consideration the differences in statistical importance of several pathology variables when predicting biochemical failure. Although most patients with pathologically confirmed status pT2a would remain progression-free after radical prostatectomy, there is a subset of 10–26% of those patients, which eventually develops progression [41,42]. ANNs could play a key role in these questions as well. In an article by Mattfeldt et al. [22], there were given some promising results by a comparison of two groups of 20 patients (with or without progression of disease) that were matched for age, preoperative PSA and duration of follow-up. The methodology of an ANN predicting cancer progression by only three variables given (Gleason score, WHO grade, tumor diameter) was used too.

Han et al. [23] reported the ability of an ANN in stratifying patients with intermediate risk as for Gleason score 7, into risk groups that differed to primary Gleason score of 4 or 3, and by so explore a hidden difference in the patient progression outcome. Ziada et al. [24] also report a better predictive outcome for their ANN, in terms of pathological stage and biochemical failure.

Similar results were reported by Potter et al. [25] in a group of patients with intermediate risk of progression (T1b–T2cN0M0, Gleason scores 5–7) by using a 'genetically' engineered ANN (GENN). Genetically stands for the fact that the ANN develops its architecture and selects the fittest solutions so that ultimately an optimal network may evolve. These authors used variables such as prostatectomy pathologic findings, age, but also DNA ploidy and quantitative nuclear grade (QNG—the variance of 41 different nuclear descriptors). There were three models of ANN according to the variables used:

(1) pathology and age;
(2) Nuclear Morphometric Descriptors and DNA ploidy;
(3) all variables included.

The accuracy of the three GENN models was 74.4%, 63.1% and 73.5% in training and 74.3%, 80% and 78.1% for testing, respectively. Data were then analyzed by Logistic Regression and Cox proportional hazards modeling finding that Logistic Regression Analysis maximized performance in the training sets only to be outperformed by the ANNs in testing sets.

Porter et al. [26] found a highest (80%) area under curve in ROC analysis, in comparison to other methods of statistical analysis, in an ANN model that was used to predict biochemical failure.

Finally, Naguib et al. [38] have demonstrated the ability of a Neural Network in correctly classifying patients' prognostic outcome according to six conventional factors (age, stage, bone-scan findings, grade, serum PSA, treatment) and two experimental markers (immunostaining for bcl-2 and p53, which are both apoptosis-regulating genes). A total of 80% of the patients were correctly classified regarding outcome using the combination of factors. When both bcl-2 and p53 immunoreactivity were excluded from the analysis, correct prediction of the outcome was achieved in only 60% of the patients ($p = 0.0032$).

3. Discussion

Oncologic decision-making has always been based on facts and predictions for individual patients. The interpretation of facts was to be made by the clinician, who therefore used his experience in order to stratify patients into risk groups and decide the best therapeutic option for them. Traditionally, statistical models of analysis have been used for this purpose. As data grew bigger, newer reports could examine a standard outcome for a larger group of people with similar characteristics. Since traditional statistics uses fixed rather simplistic correlations that require or assume linear relationships for interpreting facts, the computed out-

come can only reveal limited patterns and relationships of data, and thus it is somehow limited.

We have reviewed the basic functional characteristics of ANN methodology (training, validation and testing) and the advantages in their use. The application of ANNs in medical decision-making is a newly emerging phenomenon. For efforts in this area to be truly successful, there are a few risks to be aware of and problems to overcome when dealing with this new form of statistical analysis.

One of the key elements to using ANN technology, in medicine, is the construction of a quality medical record, that can easily be accessed and provide specific medical data in a coded way rather than a text-form. Because of the sensitive nature of the input training of ANNs, they tend to be somewhat of a trap for the unsuspected clinician. As the application of this highly sophisticated method of thinking arises, there are some serious considerations for scientists to deal with.

First of all, a clinician and possible user must have a thorough knowledge, of ANNs methodology, the quality of input data, and also the model's limitations, since reasonable fear exists to the fact that data unfit for a population might be used for decisions in another.

Also, technical differences, differences due to race, time of data collection, health care systems and their screening policies can also influence the outcome of an ANN. ANN applications should be repeatable (not single institution experiences) and therefore need to have clearly definable known in and output variables, in order to avoid single institution bias. But, even in a single institution database (if one accepts the probable bias) the experience given could reveal useful information for the local community.

Also, conventional statistics (i.e. ROC methodology), which have a long association with single factor association problems; still can be successfully applied to multifactorial classification problems. ROC methodology can be employed as to measure, report and benchmark neural network performance [1], as a means of ''reparability'' for ANN training.

A database system, which must also ensure confidentiality and encoding of medical data by common shared standards, is still under way. To be more optimistic, there lies a good opportunity as well: now that the new technology is emerging, proper databases should be constructed and be used as for input data, something that is somewhat of a disadvantage at present.

It is also an acceptable obstacle that there is going to be some slow approval especially from older clinicians that have been used to a certain way of decision-making for so many years now. Though, we might make a step forward in persuading the people of our specialty to change their ways, by the clear demonstration of the clinical beneficial effect achieved by the incorporation of such procedures.

4. Conclusion

We believe that there is some serious possibility that Artificial Intelligence, carrying the power of an easy tool that uses up-to-date data and has a flexible way of ''learning'', may provide a better oncological decision support. The availability of such data for every patient is a key issue that must be an issue of interest for health care systems to deal with, since the construction and use of electronic medical records comes with all the advantages, such as easy accessibility, and back-up technology.

Development of proper quality databases must be under construction now that hardware capabilities are more powerful and medical data is readily available. It is evident that the current state of ANNs reflects an in-part experience for disease patterns, since their application reflects specific data input, so currently, we should consider ANNs as an important tool for consultation that should never replace our personal knowledge and judgment, and by so it comes only complementary to our decision-making. It must be used as a unique for each patient risk assessment test, in order to give him the best accuracy in prediction.

Although reasonable skepticism has been expressed for the clear evidence of ANN out performance in comparison to standard statistical analysis and the methodological deficiencies of several previous studies [6,45], this diagnostic or prognostic tool can be an attractive alternative to conventional statistics since it tries to simulate a thorough way of understanding medical facts, while LR odds ratios can be calculated for each variable separately and remain easily understandable and useful.

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