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ORIGINAL ARTICLE

MODELING DIAGNOSIS THE MALIGNANT THYROID TUMOR'S WITH ARTIFICIAL NEURAL NETWORKS METHOD

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ABSTRACT: Differences between physicians' experiences as well as limitations in laboratory work ups are factors which form an obstacle so that a certain medical condition could not be solved such straight forward via following a definitive formula. Hence, artificial intelligence may be able to help doctors as a savior. In current literature, fine-needle aspiration (FNA) is the milestone whether to manage a thyroid nodule surgically or not. But its sensitivity/specificity may be that obstacle to turn a thyroid surgery into a mandatory procedure purely on behalf of attaining a definitive diagnosis in suspicious cases while the majority has benign surgical pathology. This study aims at using and training an artificial neural network (ANN) in thyroid nodule diagnosis to help the physicians have more appropriate decision-makings for the surgical team. We designed and trained an artificial neural network (ANN) on a prospectively gathered cohort, formed of 345 subjects who have underwent thyroid resection after thyroid FNA was performed on them. Prospectively, the histopathological results of surgical specimens were compared to FNA results. The preoperative FNA results matched with 63.5% of subjects when compared to surgical histopathology ones (true positivity=29.3%). The back propagation algorithm using GDM training method showed to be the most accurate predictive value with an AUC = 0.698. An extensive bio-statistically validated ANN of certain clinical as well as Para clinical and individual given inputs (predictors) has the capability to stratify the malignancy risk of a thyroid nodule to individualize patient care.

***Keywords*:** Thyroid Nodule, Fine-Needle Biopsy, Neural Networks (Computer), ROC Curve, Diagnosis

BACKGROUND

As human medical issues evolve day after day,it becomes more obvious that environmental as well as genetic diversities affect a certain condition. Furthermore, published literature makes it clear that these certain conditions could not be solved such straight forward via designing some flowcharts. Differences between physicians' experiences as well as limitations in laboratory work ups and their availability are among those mentioned diversities and factors.A considerable inevitable fact is that a certain medical disorder/disease could not be managed following a definitive cliché or formula. In such conditions computer programs (software) are born to play roles as artificial trainable brains which could give physicians a clear result based on inputs which are introduced to the program earlier in each circumstance.So an artificial program is formed in order to help physicians decide logically in quite unique medical conditions. Palpable thyroid nodules are among such challenging medical issues[1].

In current literature fine-needle aspiration (FNA) biopsies are set to be the milestone of a model which helps the physician decide whether a certain thyroid nodule needs a surgical approach or not [2]. FNA biopsy is held to be the most cost-effective but still an imperfect diagnostic tool for thyroid nodules to be evaluated in current practice [3].

A glance at the identified risk factors for the presence of carcinoma within thyroid nodules include: age, gender, prior history of neck irradiation as well as larger thyroid nodule size [1]. A considerable fact is that sensitivity and specificity of FNA varies significantly as it remains highly dependent on the operator as well as the cytologist`s skills [3]. Tee YY et al. reported sensitivity as low as 66%, but this figure approximates 80% when a comprehensive review of published literature was done. They claimed that FNA is capable of missing up to a third of all thyroid malignancies [4].

Development of the machine learning platform provides users the ability to train these networks in order to act as a smart, logic circuit to estimate the probability of a disease or disorder based on the input variables using an intuitive computer program [3]. Stojadinovic et al. showed an integrated predictive decision model using Bayesian Belief network analytical tool which compiles the joint probability distribution of all the variables in the data set by building a directed acyclic network of conditional probabilities to be significantly effective on predicting malignancy in thyroid nodules [3].

The scattered nature of clinically gathered data and analyzing their relevant variables need a compliant statistical method. The artificial neural network (ANN) is a branch of artificial intelligence. It is a nonlinear modeling method capable of finding complex relationships and patterns between large amounts of data without being disturbed by multiple variables as inputs. ANN is derived from brain neuronal architecture which could simulate how brain behaves when it predicts the antecedent event based on some detailed data input earlier.

We hypothesized that conduction of an ANN applied to certain clinical attributes could develop a malignancy risk assessment tool helping physicians to interpret the FNA biopsy results of thyroid nodules in a context composed of patient`s clinical variables known as malignancy related risk factors. We further hypothesized that an ANN derived predictive model could potentially produce a feasible decision making tool in order to help physicians predict malignancy in thyroid nodules.

Materials and Methods

This was a prospective observational cohort study evaluating the diagnostic accuracy of a preoperative malignancy risk assessment tool in patients scheduled to undergo thyroidectomy. We designed and trained an ANN on a prospectively formed cohort, gathered over a four-year period (2007-2011).

The study population was formed of 345 subjects underwent thyroid resection in Namazi and Rajaee hospitals, tertiary care centers of Shiraz University of Medical Sciencesand Rajaee hospital asa level I trauma center, Shiraz, I.R.Iran after thyroid FNA was done for them. The results of FNA and surgical specimens were analyzed and compared by experienced, board-certified pathologists without knowledge of how suspicious were FNA results for thyroid malignancy. All data mentioned above were collected via reviewing patients` files. Local institutional review board approval was obtained as well.

STATISTICAL ANALYSIS

The study data were introduced to an ANN in order to analyze and further simulate a modeling method to render the relationship between the inputs. The purpose of this modeling method is to design and train a network which could be able to assess the malignancy risk probability in a patient when certain inputs known as risk factors for thyroid malignancy are given.Hence,ithelps the physician to interpret the results of FNA biopsies in the context of other risk factors in order to minimize the unnecessary diagnostic surgeries as well as neglecting suspicious cases.

The modeling process initiates as subjects are divided into two groups randomly. The bigger group consists of 70 to 75% of patients to train the network while the rest are used to evaluate the trained network to identify its predictive value. These two groups are named the training set and the testing set respectively. In this study, a back propagation ANN composed of 10 neurons in hidden layer and 2 neurons in output layer is used that is trained via Batch Gradient Descent (GD), Batch Gradient Descent with Momentum (GDM), Gradient Descent with Adaptive (GDA).

To find the best transfer function amongst purelin, logsig and tansig functions, different combinations of these functions in hidden layer and output layer, the network was trained and tested 20 times for each protocol, and then the percentage of correct diagnosis and the time used for the training was obtained, and an average from the percentage of correct diagnosis and time used for each network was obtained finally. Then, the combination which showed the most correct percentage and the least training time amongst different cases was chosen and the ultimate network was trained via these transfer functions.

We further evaluated this neural network by Receiver-operating Characteristic curve (ROC) methods [5]. The analysis was then performed using MATLAB 7.11.0. The ROC curve method draws the probability of correct diagnosis of malignant nature of a certain thyroid nodule by the network (known as sensitivity) versus the false diagnosis of a nodule as benign one (known as false negative value or 1-specificity).The more the Area-Under-the Curve (AUC) is, the more its ability in prediction becomes.

RESULTS

We compared the preoperative FNA results with surgical histopathology ones in this study. They were matched in results in 63.5% of subjects. On the other hand, FNA biopsy had not predicted a malignant nature for thyroid nodules in 16% of circumstances (false-negative) and in 20.5% of subjects FNA was falsely positive for thyroid malignancy (table1).

Table1. True positive and true negative values for FNA biopsies versus surgical specimen analysis

FNA / Histopathology	Benign (%)	Malignant (%)
Benign (%)	118 (34.2%)	71 (20.5%)
Malignant (%)	55 (16%)	101 (29.3%)

Table 2 demonstrates the characteristics of our study population. These will form the inputs for our ANN. As a matter of fact, these descriptive data sets include thyroid malignancy risk factors as current literature notes. The output of our network is whether a nodule is benign or malignant in nature which is definitely proved by prospective review of surgical histopathology results.

Table2.Descriptive characteristics of study population

Variable	Frequency (percentage)
Gender	Male = 66 (19.1%)
	Female = 279 (80.9%)
Having multiple nodules	Yes = 182 (52.8%)
	No = 163 (47.2%)
Rapid growth	Yes = 251 (72.8%)
	No = 94 (27.2%)
Family history of thyroid disease	Positive = 60 (17.4%)
	Negative = 285 (82.6%)
Family history of malignancy	Positive = 61 (17.7%)
	Negative = 284 (82.3%)
Age	≤36 y/o = 136 (39.4%)
	>36 y/o = 209 (60.6%)
Size of thyroid gland	≤5.5 cm = 153 (44.3%)
	>5.5 cm = 192 (55.7%)
Size of thyroid nodule	≤2 cm = 230 (66.7%)
	>2 cm = 115 (33.3%)
Years of disease involvement (disease duration)	≤1.5 yrs. = 175 (50.7%)
	>1.5 yrs. = 170 (49.3%)
Nature of disease	Benign = 189 (54.8%)
	Malignant = 158 (45.2%)

We administered different algorithms to train the network. As it is revealed in table 3, the median percentage of current predictive value of the network is calculated following 20 rounds of network training.

Table3.Median percentage of correct predictive value of network following 20 rounds of training and best transfer function in hidden layer and output layer

Training algorithm	Transfer function in Hidden layer	Transfer function in Output layer	Median accuracy percentage
GD	purelin	purelin	62.81%
GDM	tansig	purelin	60.48%
GDA	purelin	purelin	60.16%

Based on ROC curve evaluation method, the back propagation network with GDM training algorithm has the most accurate predictive value with an AUC = 0.698(table 4).

Table4. AUC of ROC based on different training algorithms

Training algorithms	ROC curve evaluation method				
	AUC	Standard deviation	P-value	95% Confidence Interval	
				Lower Bound	Upper Bound
GD	0.677	0.068	0.015	0.544	0.810
GDM	0.698	0.068	0.007	0.564	0.831
GDA	0.689	0.067	0.010	0.558	0.820

DISCUSSION

The aim of current study was to introduce a bioinformatics-derived preoperative malignancy risk assessment model using a prospective observational cohort study in order to evolve an ANN based risk stratification tool, unique for each and every patient who is pre-determined to undergo thyroid resection.

Thyroid nodules are quite common findings among patients who seek medical help in the U.S. however, the majority of palpable nodules are found to be pathologically benign in nature later on at the surgical histopathology reports. FNA is currently the initial diagnostic workup with a significantly diverse sensitivity and specificity highly dependent on the operator as well as the cytologist`s skills. But a worth-noting fact is that more than 20% indeterminate FNA biopsy results that push the surgeon to consider some kind of thyroidectomy purely in behalf of achieving a clear diagnosis and ruling out a questionable malignant nodule.

We applied the ANN on a prospectively gathered clinical data including Para clinical, clinical, individual as well as histopathological predictors for malignancy. Later on, a subject-individualized malignancy risk stratification neural network was designed, evolved and cross-validated in order to clarify a patient-specific malignancy risk prediction model in thyroid nodules.

Based on ROC curve evaluation method, the best network trained by our clinical dataset was the one with back propagation algorithm using GDM training method. According to this trained network, the most important risk factors in malignancy of thyroid nodules arerespectively: A positive family history of thyroid disease,malignant nature of FNA biopsy result,having multiple nodules, disease duration > 1.5 years,a positive family history of malignancy, rapid growth of thyroid nodule(s),size of thyroid nodule > 2 cm, age > 36 years old, size of thyroid gland in physical examination > 5.5 cm and gender. Based on these findings, the clinician would be able to decide to go on a surgical plan for a certain given subject considering the FNA biopsy results the number of risk factors noted as well as their priority.

One advantage of modeling by artificial neural network is its ability to describe the vague and complicated relations between the clinical findings without any special assumptions about their counts and nature. The only important point in its modeling process is the size of dataset. The larger the data set is, the better the network is trained. Therefore, its accuracy rate in diagnosis will be increased. Accordingly, the role of each mentioned risk factor in prediction of thyroid nodules malignancy would be better discovered in a larger study with more data.

CONCLUSION

Our work is strongly in agreement with these findings in that an extensive bio-statistically validated artificial neural network of certain clinical as well as Para clinical and individual given inputs (predictors) has the capability to stratify the malignancy risk of a thyroid nodule in order to individualize patient care. This risk assessment model (tool) could virtually minimize the unnecessary diagnostic thyroid surgeries as well as FNA misleading.

This new born yet promising risk stratification tool definitely warrants further validation through experimental trials. We claim that this model could be easily accessed by physicians via an application (software) and utilized by surgeons as well to assess the malignancy risk of thyroid nodules in specific subjects.

CONFLICT OF INTEREST

Authors declare that they have no conflict of interest.

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