A comparison of logistic regression and artificial neural networks in predicting central lymph node metastases in papillary thyroid microcarcinoma

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OBJECTIVE: *Prophylactic central lymph node dissection(CLND) is a controversial issue in papillary thyroid microcarcinoma(PTMC) patients without lymphatic metastasis. Artificial neural network(ANN) has been proposed as an alternative statistical technique for predicting complex biologic phenomena. Our aim is to develop an ANN model in predicting central lymph node metastases(CLNM) in patients with PTMC, in comparison to traditional logistic regression(LR) analysis.*
STUDY DESIGN: *Eighty patients who underwent total thyroidectomy plus CLND for PTMC were included in the study. The factors associated with CLNM were determined by using both ANN model and LR analysis. The predictive performances of these two statistical models were compared.*
RESULTS: *Twenty (25%) patients had CLNM. In univariate analysis, age >45 years, tumor diameter >7 mm, and multifocality were the associated parameters with CLNM. These parameters were used to create LR and ANN models. LR test revealed tumor diameter >7 mm and multifocality as independent factors for CLNM. ANN (AUC: 0.786) had a higher predictive value for CLNM, in comparison to LR model (AUC: 0.750).*
CONCLUSIONS: *Tumor diameter >7 mm and multifocality are the independent prognostic indicators of CLNM in patients with PTMC. ANN model has higher predictive value for determining central metastasis, in comparison to LR analysis.*

KEY WORDS: Artificial neural networks, Central lymph node metastasis, Logistic regression, Papillary thyroid microcarcinoma.

Introduction

When Papillary thyroid carcinomas (PTCs) equal to or less than 1 cm, they are defined as papillary thyroid microcarcinomas (PMCs). Although these small tumors have an excellent overall prognosis with an estimated 5-year survival of 97%, central lymph node metastasis (CLNM), which is found in 40–60% of patients with PTC, is known to be associated with increased local recurrence rates and reduced survival [1].
Whether routine central lymph node dissection (CLND) should be necessary in the PTMC patients without evident of CLNM is a more controversial topic. One important reason is that prophylactic CLN dissection seems to have little prognostic value and to increase the frequency of postoperative transient hypocalcaemia. [2,3] Because of this evaluation of clinicopathologic factors that can cause CLNM have clinical significance. Preoperative ultrasonography (US) has limited influence to reveal LNM in the central compartment. Recently, a novel parameter BRAFV600E mutation for pre-operative risk estimation could be extremely valuable in the management of PTMC [2,4].
Recently, artifical neural networks (ANNs) has been proposed alternative for predicting complex biologic phenomena instead of standard statistical techniques. This technique inspired from working biological neuro [5-7]. Briefly, ANNs are a class of nonlinear mathematical models that are characterized by a complex structure of interconnected computational elements, the neurons. These computational elements aggregate a series of inputs by

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using a summation operation and produce an output, such as the prediction of malignancy [8].

In this study, we aimed to develop an ANN model to prediction of CLNM in patients with PTMC, and to compare the predictive performances of this ANN model and the traditional LR model.

Material and Methods

Data Collection

All patients underwent total thyroidectomy and central CLND. Patient's medical records including age, sex, tumour diameter, pre-operative serum thyroid-stimulating hormone level, thyroid hormone level, thyroid hormone therapy, final pathologic diagnosis and presence of CLNM were collected retrospectively.

Training and Validation Data Sets

Training group of patient which has nearly 70% of all patients (56 patients) were randomly selected for constructing ANN and LR prediction models. Validation group has been composed from remaining 30% patients (24 patients) and used for performance comparisons of ANN and LR models. When the proportion of CLNM was considered the training and validation groups were similar.

LR Modelling

A feed-forward stepwise algorithm was used to construct the multivariate LR model [8].

ANN Modelling

To find patterns in data or to model complex relationships between inputs and outputs the ANN can be used as nonlinear statistical data modeling tool. The processing elements or nodes are arranged in "input," "hidden and output" layers, each layer containing one or more nodes. "Input, hidden and output" layers have been prepared from processing elements or nodes and each layer consist one or more nodes The data which has value for predicting the outputs model have located at input layer. Each data point is represented by a node in the input layer. Nodes were symbolized with separate data points in the input layer. The output layer predicts the possible outcome with designated model. Each node in the hidden layer is connected to every node in the input and output layer and every layer contains one or more processing layer all interconnected. Each connection carries a "weight" or value that determines the relevance of a particular input for the resulting output. The strength of connections between the neurons in the input, hidden and output layers determines the ANNs predictions. The results of the output layer in ANNs model represent the probability of a characteristic of interest (CLNM) [8].

We used the variables that elected by the univariate analysis. IBM SPSS Statistics 19 were used to build three-layered ANN with backpropagation circuit. Applying back-propagation allows a model that starts with known inputs and random outputs to be trained until the ANNs output values match the expected output. Four "hidden" neurons were used. The ANNs was iterated in excess of 100,000 epochs for the training with 80.8% accuracy. Batch learning process was used.

Statistical Analysis

Model discrimination was measured by the area under the curve (AUC) the receiver-operator characteristic (ROC) curve to evaluate how well the model distinguished patients experienced the events from those who did not. An AUC of 0.5 indicates that the model does not predict better than chance. The discrimination of a diagnostic model is considered perfect if AUC is equal to 1, good if AUC is greater than 0.8, moderate if AUC is 0.6-0.8 and poor if AUC is lesser than 0.6 [8] . ROC curves were compared using paired T-tests.

Results

General Patient Characteristics

The median age of the patients was 44 years (min: 18- max: 75 years). About 71 (88.8%) were female and 9 (11.2%) were male patients. The median size of primary tumor was 0.64 cm (IQR: 0.45-0.95 cm). Multifocality and capsular invasion were found in 25 (31.3%) and 22 (27.5%) patients, respectively. Final pathology revealed CLNM in 20 (25%) patients.

Univariate and Multivariate Analyses for Clnm

Median age of patients with CLNM was 37 (min: 18- max: 59 years) while median age of the patients without CLNM was 46 (min: 18- max: 75 years). The patients with CLNM had a median tumor diameter of 0.8 cm (IQR: 0.45-0.95 cm); whereas median tumor diameter was 0.6 cm (IQR: 0.5-0.8 cm) in patients without CLNM. Multifocality rate was 50% in patients with CLNM and 18.5% in patients without CLNM. Multicentricity rate was 42.8% in patients with CLNM and 16.9% in patients without CLNM. Capsule invasion was present in 40% of patients with CLNM. Capsule invasion was present in 24.1 % of patients without CLNM.

TABLE I - *The comparison of clinicopathological factors between the patients with CLN metastasis and patients without CLN metastasis*

Characteristics	**Patients with CLNM(n=20)**	**Patients without CLNM (n=60)**	**P**
Age (y)	37 (18-59)	46 (18-75)	0.527
Age (categorical)			**0.019**
Age ≤45	16 (80%)	29 (48.4%)	
Age >45	4 (20%)	31 (51.6%)	
Gender			0.339
Female	16 (76.2%)	53 (89.8%)	
Male	5 (23.8%)	6 (10.2%)	
Tumor size (mm)	8 (4.5-9.5)	6 (5-8)	0.067
Tumor size (categorical)			**0.031**
≤7 mm	8 (40%)	42 (70%)	
>7 mm	12 (60%)	18 (30%)	
Multifocality			**0.012**
Unifocal	9 (45%)	46 (76.7%)	
Multifocal	11 (55%)	14 (23.3%)	
Multicentricity			0.194
Absent	14 (70%)	50 (83.4%)	
Present	6 (30%)	10 (16.6%)	
Capsular invasion			0.399
Absent	13 (65%)	45 (75%)	
Present	7 (35%)	15 (25%)	

Data are presented as median (IQR) for age and tumor size; n (%) for other variables. y: year, mm: millimeter, IQR: Interquartile range

TABLE II - *Multivariate analysis (Binary logistic regression test) of CLN metastasis*

Variables	**β (SE)**	**p**	**Exp (β)**	**95% CI of Exp (β)**
Age (categorical)	1.243 (0.65)	0.058	3.46	0.95-12.5
Tumor size (categorical)	-1.311 (0.58)	**0.026**	0.27	0.08-0.85
Multifocality	-1.312 (0.59)	**0.027**	0.26	0.08-0.85
Constant	-0.390 (0.73)			

SE= Standard error, Exp ( )= Odds ratio, CI= Confidence interval

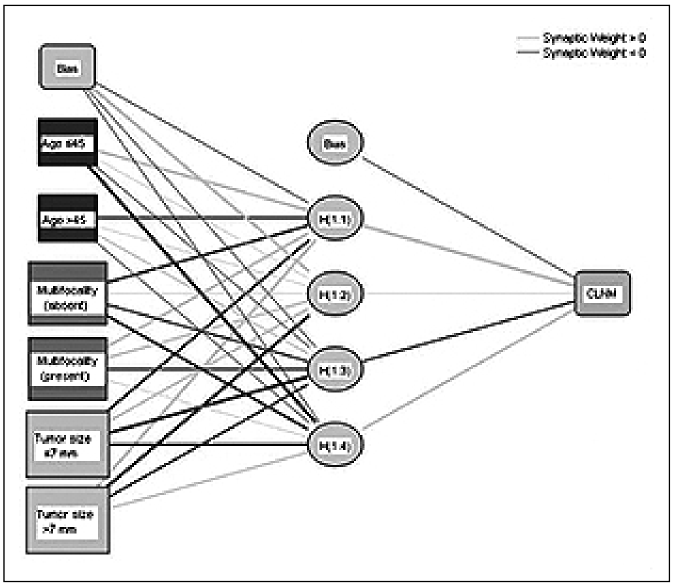

Fig. 1: Schematic representation of the ANN model for CLNM in patients with PTMC.

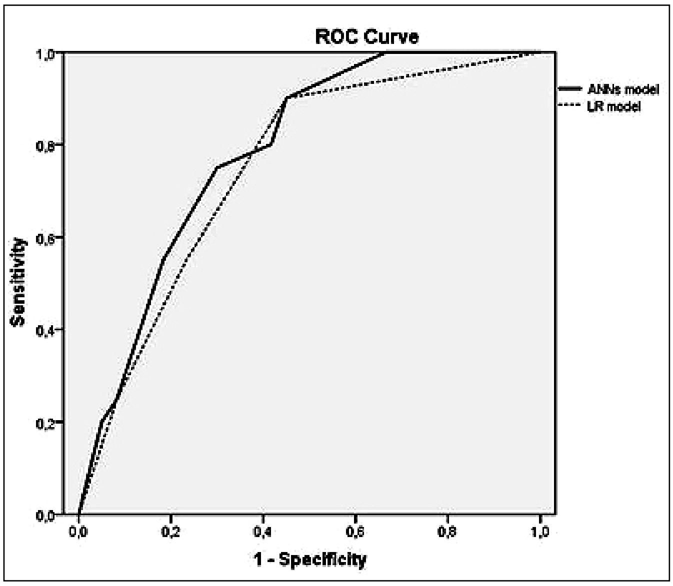

Fig. 2: Receiver operating characteristic (ROC) curves of ANNs (validation data) (AUC: 0.786) and LR models (AUC: O.750) to predict CLNM in patients with PTMC.

In univariate analyses; the following variables were statistically significant: Patient age (≤45 years,), tumour diameter (>7mm), and multifocality (Table I). These parameters were used to create logistic regression and ANN model.
In multivariate analysis, tumour diameter (≤7mm, >7mm) and multifocality were found to be independent predictors for CLN metastasis (Table II).

ANALYSIS OF ANN

The following three parameters which were found to be associated with CLNM in univariate analysis were used to build an ANN model: age (≤45 years), tumour diameter (>7mm), and present of multifocality. Multilayer perceptron, a widely used ANN architecture, was used to establish this ANN model. In the present study, multilayer perceptron included three input nodes and one output node (CLNM). Then, four hidden neurons were added to the hidden layer to increase the performance of multilayer perceptron. Finally, the neurons were linked with weighted connections (Fig. 1).

Comparison of Models

Logistic regression model and ANN achieved AUCs of 0.750 (%95 CI: 0.684-0.899) and 0.786 (%95 CI: 0.634-0.866), respectively. The ANNs model could predict an individual's risk of having CLNM successfully (p= 0.005). Fig. 2 summarizes the ROC curve obtained from the ANNs and LR models.

Discussion

We found that the performance of the scoring system was improved significantly by the ANN when the same information was given. ANN, or simply neural network, is a machine learning method evolved from the idea of simulating the human brain. Compared to a traditional regression approach, the ANN is capable of modeling complex nonlinear relationships [9]. ANN technique has gained popularity in medical decision-making in various disciplines of medicine, and has become an alternative or supportive statistical method to the traditional LR model which is stil the most commonly used method for developing predictive models for dichotomous outcomes in medical researches [10,11]. Cancer is one of the most commonly studied medical field in this manner. To date, many clinical researches focused on the comparison of ANN model and LR model have been reported in the literature. ANN model was most often found similar or superior to LR analysis in those studies. [12-15] It should be stated here that ANN was reported to have higher prediction rates in complex and non-linear relationships among a large number of variables when compared with LR model. For example, in a study aimed to predict the operative mortality in 18,362 patients undergoing cardiac surgery, ANN was found to have higher ROC curve than that of the LR model with the selected 34 risk variables [16]. On the other hand, in another study including 202,932 cases with 17 variables, ANN and LR had similar ROC curves [12]. In addition, these two statistical models showed similar performances in the studies with small number of variable [17,18]. However, ANN was not found to be inferior to LR in most of the studies comparing the performances of these two statistical models. Our study also included small number of cases with eight variables, but clearly demonstrated the higher predictive value of ANN in comparison to LR.

Although the primary goal of the present study was the comparison of ANN and LR analysis in predicting CLNM in PTMC, the clinicopathological factors associated with CLNM were also tried to determine. It is known that total thyroidectomy plus therapeutic CLN dissection is the standart surgical approach for patients with PTMC and involved lymph nodes. However, prophylactic central dissection in patients without clinical and radiological evidence is still a controversial issue due to some concerns such as temporary hypocalcemia, permanent hypoparathyroidism, and recurrent laryngeal nerve injury might outweigh its prognostic benefit. Actually, these surgical complications, except temporary hypocalcemia, do not increase with prophylactic central dissection [19]. The rate of temporary hypocalcemia was similar to previous reports [19,20]. The rates of other complications were also in parallel to the current literature. It should be also stated here that involvement of central compartment is one the most important risk factors of recurrence. Thus, removal of subclinical metastasis decreases the recurrence rate, and improves the prognosis. In addition, CLND avoids reoperation which is a technically challenging procedure with an increased risk of surgical morbidity.

It is fact that most of CLN metastases are less than 5 mm, and cannot easily detected by standard imaging methods [21]. Ijn the present study, CLNM was found in 25% of the patients, consistent with the literature [22,23]. Therefore, determination of predictive factors associated with CLNM is of great importance in PTMC. To date, many clinical and pathological factors such as age, gender, tumor size, and multifocality were reported to be predictors of CLNM in patients with PTMC. However, there is not a global consensus on this topic. For example, some authors reported that age at the time of diagnosis was an independent predictor of CLNM in PTMC while others did not find and association between age and presence of central involvement [24,25]. However, a cutoff age of 45 years is widely used as a prognostic indicator [26]. Similarly, being under 45 years old was shown to be an associated factor for CLNM in our study. In addition to age, tumor diameter higher than 7 mm and multifocality were the other associated parameters of CLNM in univariate analysis. These two parameters were also determined as independent risk factors of CLNM in multivariate analysis. In similar, tumors larger than 5 mm were found to be associated with increased risk of CLNM in previous works [24,27]. Multifocality is another factor related to involvement of central compartment, and is found in approximately 35% of the patients with PTMC [24,25,28]. Other factors such as gender and extracapsulary invasion were also reported as predictors of CLNM in PTMC [4,24]. In our study, no association between these parameters and CLNM was found.

In all the clinical studies above mentioned, traditional LR analysis was used to determine the associated predictive factors of CLNM in patients with PTMC. In this manner, the present study is the first to show the higher predictive value of ANN compared with LR analysis. ANN has several advantages such as requiring less formal statistical training, ability to implicitly detect complex nonlinear relationships between dependent and independent variables, ability to detect all possible interactions between predictor variables and the availability of multiple training algorithms [29,30]. On the other hand, there are also some disadvantages related to ANN use.

First of all, a long training process and an experienced user are needed to evaluate the optimal network topology. The number of hidden layer nodes is of great importance for the proper training. While the neural network is over-trained with using too many hidden nodes, proper training is impeded in case of too few nodes are used [13]. The poor interpretability of selected models may be also considered as another limitation of ANN technique. Namely, standardized coefficients and/or odd ratios related to selected variable cannot be calculated as in regression models. In this situation, logistic regression tests can be applied to overcome the statistical problem due to improved interpretation of individual predictors.
In conclusion, tumor diameter higher than 7 mm and multifocality are the independent prognostic indicators of CLNM in patients with PTMC. ANN model has higher predictive value for determining central metastasis, in comparison to LR analysis. On the other hand; ANN model has a risk of overfit because of the nonlinearity. We suggest that this technique may be helpful to take a decision for central compartment dissection in patients with PTMC.

Riassunto

La dissezione linfonodale centrale profilattica (CLND) è una argomento controverso da eseguirsi in pazienti con microcarcinoma papillare della tiroide (PTMC) in assenza di metastasi linfatiche. È stato proposto l'uso della rete neurale artificiale (ANN) come tecnica statistica alternativa per la predizione di fenomeni biologici complessi. Il nostro scopo è quello di sviluppare un modello di rete neurale artificiale (ANN) per la previsione della presenza di metastasi linfonodali centrali (CLNM) in pazienti con microcarcinoma papillare della tiroide, e confrontarlo con la tradizionale analisi di regressione logistica (LR).
Lo studio si è avvalso di 80 pazienti sottoposti a tiroidectomia totale con CLND per PTMC, determinando i fattori associati com CLNM usando sia il modello di rete neurale artificiale e l'analisi di regressione logistica, paragonando l'efficacia predittiva di questi due modelli statistici.
In 20 pazienti (25%) si è riscontratta la presenza di matastasi nei linfonodi centrali. con l'analisi univariata l'età superiore ai 45 anni, il diametro del tumore supeirore ai 7 mm e la multifocalità si sono dimostrati parametri associati con la presenza di questa metastatizzazione. Questi parametri sono stati usati per crearemodelli di regrassione logistica e di rete neurale artificiale. 1 test di regressione logistica ha rivelato come fattori indipendenti per la metastatizzazione linfonodale centrale sia il diametro tumorale superiore a 7 mm che la multifocalità. La rete neurale artificiale (AUC: 0,786) ha dimostrato un superiore valore previsionale per la metatstatizzazione linfonodale centrale rispetto al modello di regressione lineare (AUC: 0,750).
In conclusione il diametro tumorale superiore a 7 mm e la multifocalità sono gli indicatori prognostici indipendenti della metastatizzazione linfonodale centrale di microcarcinomi papilliferi della tiroide, e il modello di rete neurale artificiale dimostra un maggiore valore predittivo rispetto alla analisi di regressione lineare per questa metastatizzazione.

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