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Original Article

Artificial neural network for predicting pathological stage of clinically localized prostate cancer in a Taiwanese population

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Abstract

Background: We developed an artificial neural network (ANN) model to predict prostate cancer pathological staging in patients prior to when they received radical prostatectomy as this is more effective than logistic regression (LR), or combined use of age, prostate-specific antigen (PSA), body mass index (BMI), digital rectal examination (DRE), trans-rectal ultrasound (TRUS), biopsy Gleason sum, and primary biopsy Gleason grade.

Methods: Our study evaluated 299 patients undergoing retro-pubic radical prostatectomy or robotic-assisted laparoscopic radical prostatectomy surgical procedures with pelvic lymph node dissection. The results were intended to predict the pathological stage of prostate cancer (T2 or T3) after radical surgery. The predictive ability of ANN was compared with LR and validation of the 2007 Partin Tables was estimated by the areas under the receiving operating characteristic curve (AUCs).

Results: Of the 299 patients we evaluated, 109 (36.45%) displayed prostate cancer with extra-capsular extension (ECE), and 190 (63.55%) displayed organ-confined disease (OCD). LR analysis showed that only PSA and BMI were statistically significant predictors of prostate cancer with capsule invasion. Overall, ANN outperformed LR significantly (0.795 ± 0.023 versus 0.746 ± 0.025, $p = 0.016$). Validation using the current Partin Tables for the participants of our study was assessed, and the predictive capacity of AUC for OCD was 0.695.

Conclusion: ANN was superior to LR at predicting OCD in prostate cancer. Compared with the validation of current Partin Tables for the Taiwanese population, the ANN model resulted in larger AUCs and more accurate prediction of the pathologic stage of prostate cancer.

Keywords: artificial neural network; capsule invasion; Partin Tables; prostate neoplasm

1. Introduction

Radical prostatectomy (RP) is the most effective therapy for adeno-carcinoma of the prostate when the cancer is either organ- or specimen-confined at the time of operation.[1–3] Therefore, it is beneficial for patients with prostate cancer and their physicians to be able to predict the pathologic stage of the disease before surgery. In 1997, Partin et al[4] used a

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combination of prostate-specific antigen (PSA) expression analysis, clinical classification, and the Gleason score to predict the pathologic stage of localized prostate cancer in a multi-institutional study. However, the predictive values of the current Partin Tables, which were updated in 2001[5] and 2007,[6] have not been validated in most Asian populations, including Taiwan.

We developed the artificial neural network (ANN) using readily available clinical data to improve the prediction of prostate cancer staging compared with currently available staging methods. ANN is a computer modeling approach based loosely on the function of a biological neuron and its relationship to a neural network. In this study, we performed a cross-sectional investigation to develop ANN for predicting the final pathologic stage of prostate cancer in patients who had undergone RP. The results were compared with two other predictive models: a logistic regression (LR) model and the 2007 Partin Tables. To our knowledge, this is the first study to use an ANN model to predict the pathologic stage of prostate cancer in a Taiwanese population, which also allows a comparison with the existing LR method and to further validate the current Partin Tables.

2. Methods

In this study, we used pathologic and clinical data taken at the time of prostate biopsies to develop and test an ANN model for predicting the final pathologic stage of disease. Then, we compared ANN with two other modeling techniques, where one model employed multivariate LR and the other the Partin Tables, as described in previous studies. Patients enrolled in the study had all undergone an RP surgical procedure at Tri-Service General Hospital, Taipei, Taiwan from September 2001 to April 2012. The final cohort study, consisting of 299 patients, was randomly divided into two mutually exclusive datasets: the training set and testing set. Written informed consent was obtained from all patients and the study protocol was approved by the appropriate ethics committees.

Discussions with several urologists revealed which variables they believed were most significant in determining the pathologic result of prostate cancer after the radical prostatectomy procedure. The resulting list of seven variables included PSA expression, age, body mass index (BMI), digital rectal examination (DRE), trans-rectal ultrasound (TRUS), biopsy Gleason sum, and primary biopsy Gleason grade. Among these variables, only DRE and TRUS were categorical classifications. The positive findings of DRE and TRUS were defined as a palpable hard nodule assessed via the digital rectal examination and a hypoechogenic lesion via the trans-rectal ultrasound image. The final report was dependent upon whether the capsule invasion of the prostate cancer was detected in the pathological specimen [organ-confined disease (OCD) or with extra-capsular extension (ECE)].

In this study, ANNs were generated using the software package STATISTICA Neural Networks (Release 7.0 E) from StatSoft Inc. Various formulations were used to train and predict the likelihood of capsule invasion of prostate cancer after radical prostatectomy from the seven independently predictive variables mentioned above. Different network architectures tested included linear networks, multilayer perceptrons, and radial basis function networks.

The dataset was randomly divided into two separate groups: 225 patients (~75%) as the training set and 74 patients (~25%) as the testing set. As no well-established theoretical method exists for designing an ideal ANN, and the optimal number of hidden nodes and iterations are unknown, the best designs are typically determined through trial and error. All models were evaluated with the testing set to determine their accuracy in predicting patients that require RP procedures.

A multivariate LR model was developed using SPSS version 13.0 (SPSS Inc., Chicago, IL, USA). All of the variables were unconditionally entered into the LR equation as they were already deemed significant in the second step of the variable selection process. The predictor variables were: (1) total serum PSA levels prior to radical surgery, which were categorically divided into 0–2.5 ng/mL, 2.6–4.0 ng/mL, 4.1–6.0 ng/mL, 6.1–10 ng/mL, and >10 ng/mL; (2) TNM clinical stage,[7] which was categorically divided into T1c, T2a, T2b, or T2c; and (3) biopsy Gleason score sum, which was divided categorically into 2–4, 5–6, $3 + 4 = 7$, $4 + 3 = 7$, and 8–10. We validated our cases against the current Partin Tables[6] to predict the final pathological stage (OCD or ECE). According to a detailed overview of each of the probability intervals (1%, 2%, etc. up to 99%), we obtained different predicted results plotted as a receiver operating characteristic (ROC) curve.

The result of the LR and ANN predictive models on a per patient basis was plotted as ROC curves. The area under the ROC curves (AUCs) with a 95% confidence interval (CI) was used as a quantitative measure of the ability of the predictor models to distinguish between responders and non-responders.

3. Results

For the 299 participants, the mean age was 66.11 ± 7.61 years (range 49–78 years), the mean baseline BMI was 24.86 ± 3.71 kg/m^2, the mean PSA expression was 16.26 ± 17.88 ng/mL, the mean biopsy Gleason sum was 6.82 ± 1.22, and the primary biopsy Gleason grade was 3.37 ± 0.69. Of the participants, 109 (36.45%) displayed prostate cancer with ECE and 190 (63.55%) showed OCD. Among the ECE and OCD groups, positive DRE rates were 30.3% and 15.8%, respectively, and positive TRUS ratios were 33.0% and 18.9%, respectively. Except for the age factor, the independent variables including BMI, PSA, biopsy Gleason sum, primary biopsy Gleason grade, positive rate of DRE, and TRUS were statistically significantly higher in the ECE than in the OCD groups (Table 1). From the results of initial ANN analyses, we found that the standard feed-forward, fully-connected, back-propagation neural network with 16 hidden nodes provided the optimal network architecture.

In this model, the hyperbolic and logistic functions were used as an activation function in the hidden and output layers, respectively. Most continuous variables including BMI, PSA,

Table 1
Comparison of a range of parameters between prostate cancer (PC) with extracapsular extension (ECE) and organ-confined disease (OCD).

	PC with ECE (n = 109)	PC with OCD (n = 190)	p
Continuous variables			
Age	66.65 ± 7.56	65.79 ± 7.65	0.350
BMI	25.71 ± 4.87	24.37 ± 2.74	0.002
PSA	23.45 ± 22.20	12.13 ± 13.24	<0.001
Biopsy Gleason sum	7.22 ± 1.38	6.59 ± 1.06	<0.001
Primary biopsy Gleason grade	3.58 ± 0.76	3.26 ± 0.62	<0.001
Categorical variables			
DRE (+)	33 (30.3)	30 (15.8)	0.005
TRUS (+)	36 (33.0)	36 (18.9)	0.009

Data are presented as n (%) or mean ± SD.
BMI = body mass index; DRE = digital rectal examination; OCD = organ-confined disease; PC = prostate cancer; PSA = prostate-specific antigen; TRUS = trans-rectal ultrasound.

biopsy Gleason sum, and primary biopsy Gleason grade were shown to be statistically significant when applying the univariate logistic regression model ($p = 0.005$, $p < 0.005$, $p < 0.001$, $p < 0.001$). The categorical variables including DRE and TRUS also showed statistically influence on the final pathologic report with OCD or ECE ($p = 0.004$, $p = 0$ .007). When multivariate logistic regressions were analyzed after adjusting other risk factors, only PSA ($p = 0.001$) and BMI ($p = 0.023$) had a statistical role in the prediction of the final prostate cancer pathological stage (Table 2). The classification threshold for the predicted values was optimally set to 0.491. The entropy function was used to estimate the error. From our statistical result, the overall accuracy rate of the ANN was 65%, which was higher than LR at 60% and magnetic resonance imaging (MRI) at 61%. The sensitivity rates for ANN, LR, and MRI prediction were 83%, 70%, and 43%, respectively, and the specific rates were 56%, 56%, and 73%, respectively (data not shown). In other words, our study results show that the clinical image tool for prostate cancer staging, MRI, revealed poorer predictive ability than previous ANN and LR models.

Using the AUCs as a measure of predictive model performance, overall ANN outperformed LR to a statistically significantly extent (0.795 ± 0.023 versus 0.746 ± 0.025, $p = 0.016$; Fig. 1A). The internal validation of ANN in testing patients also showed better performance than the LR predictive model (0.735 ± 0.051 versus 0.65 ± 0.055, $p = 0.093$, Fig. 1B). We next performed validation of the current Partin Tables[6] using the data collected from Taiwanese patients at a single center, according to clinical stage, PSA expression levels, and Gleason score sum. We analyzed the sensitivity and specificity rates according to previously mentioned forward order categorical probabilities (1%, 2%, etc. up to 99%, 100%) for all the patients, then applied the Partin Table model and an AUC of 0.695 was obtained (Fig. 2). Validation of this clinically applied model revealed a poorer predictive capacity compared with the ANN and LR models.

Table 2
Univariate and multivariate logistic regression (LR) analyses for prediction of prostate cancer pathological stage.

Variables	Univariate LR OR (95% CI)	p	Multivariate LR OR (95% CI)	p
Age	1.02 (0.98–1.05)	0.349	1.01 (0.97–1.04)	0.645
BMI	1.13 (1.04–1.22)	0.005	1.10 (1.01–1.0)	0.023
PSA	1.05 (1.03–1.07)	<0.001	1.03 (1.02–1.05)	0.001
Biopsy Gleason sum	1.57 (1.27–1.94)	<0.001	1.22 (0.86–1.73)	0.257
Primary Gleason grade	2.00 (1.39–2.86)	<0.001	1.17 (0.64–2.14)	0.610
DRE (P vs N)	2.32 (1.32–4.00)	0.004	1.39 (0.61–3.13)	0.438
TRUS (P vs N)	2.13 (1.23–3.57)	0.007	1.28 (0.59–2.78)	0.528

BMI = body mass index; DRE = digital rectal examination; PSA = prostate-specific antigen; TRUS = trans-rectal ultrasound.

4. Discussion

Oesterling et al[1] initially attempted to predict the pathologic stage of clinically localized prostate cancer using LR. In 1993, Partin et al[2] developed an LR-based nomogram for predicting the final pathologic stage. They combined the PSA expression level, clinical classification, and the Gleason score

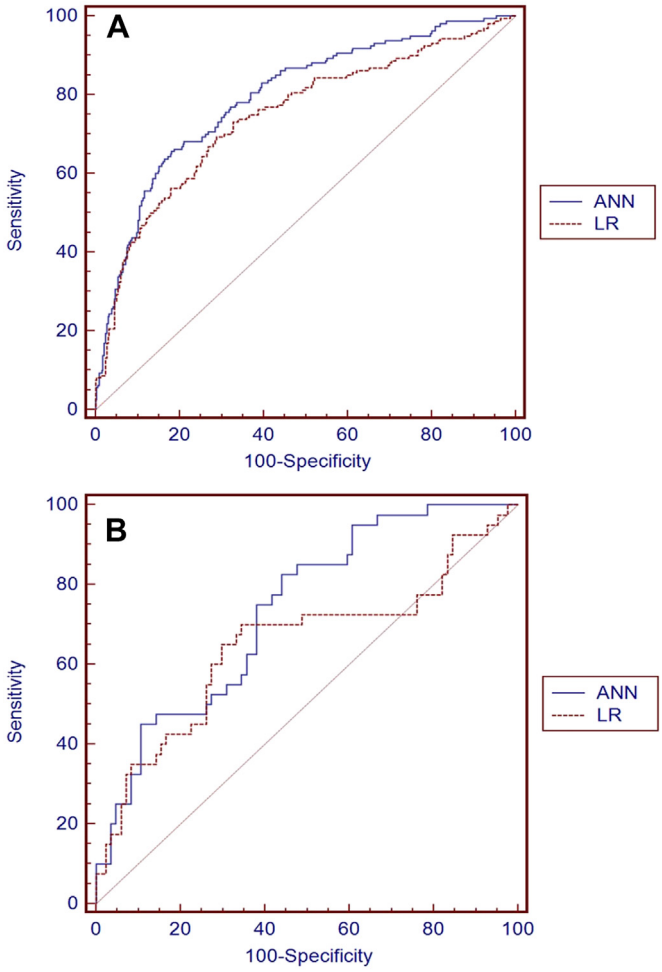
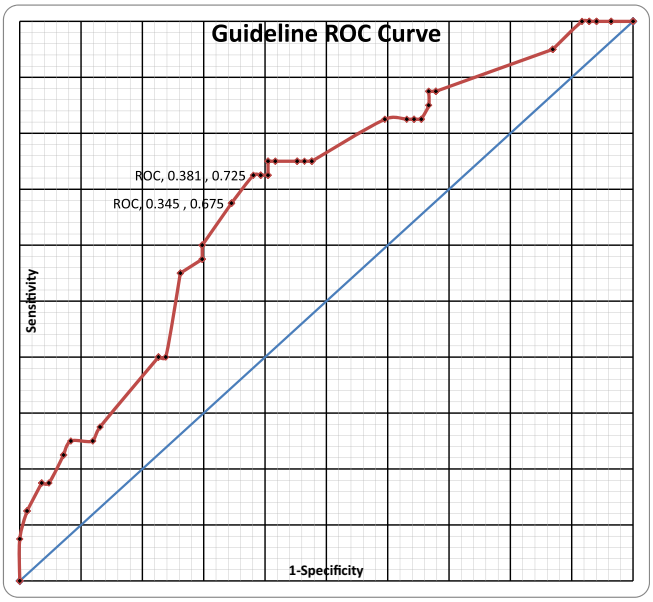


Fig. 1. (A) The predictive model of ANN overall outperformed LR overall significantly (0.795 ± 0.023 versus 0.746 ± 0.025; $p = 0.016$, $n = 299$). (B) The predictive ability of ANN testing outperformed LR testing (0.735 ± 0.051 versus 0.65 ± 0.055; $p = 0.093$, $n = 74$). ANN = artificial neural network; LR = logistic regression.



Probability (%)	10	20	30	40	50	60	70	80	90
Sensitivity	0.128	0.266	0.551	0.679	0.743	0.752	0.853	0.945	1
1-specificity	0.005	0.058	0.259	0.355	0.423	0.534	0.714	0.899	0.974

Fig. 2. The study of 299 cases validated the clinical Partin Tables and the predictive ability of AUC showed 0.695. AUC = areas under the receiving operating characteristic curve; ROC = receiver operating characteristic.

to predict the pathologic stage in males treated for clinically localized prostate cancer by a single surgeon at Johns Hopkins Hospital (Baltimore, MD, USA). Partin et al[5,6] subsequently combined the clinical data from three academic institutions and updated the LR-based nomogram to simultaneously predict the pathological stage.

ANNs and logistic regression have become two of the fastest growing and most effective systems in prostate cancer diagnosis. ANN is also an adaptive computational model designed to mimic the interconnected neurons of the brain, whose properties change when external or internal information flows through the network.[8] ANNs belong to the back-propagation class of neural networks in which models use training methods to minimize errors. ANNs are normally divided into three parts: input, hidden, and output layers of neurons whereby the inputs of each neuron are "weighted" by certain coefficients. Rosenblatt[9] first used ANNs in clinical radiology in 1958, and its use in urologic decision making was first described by Snow et al.[10]

In 1998, Tewari and Narayan[11] developed ANN models for pretreatment staging of prostate adenocarcinoma in 1200 males for the detection of ECE in patients with clinical OCD. Input variables included age, race, rectal examination findings, size of gland using ultrasound, serum PSA levels, systemic biopsy-based staging information, perineural infiltration data, and Gleason score from biopsy. In a side-by-side comparison, Borque et al[12] found a greater AUC for ANN than for a logistic regression model for predicting extraprostatic disease in a population of >400 males, although this result was not statistical significance ($p = 0.1$). Veltri et al[13] similarly found only a marginal advantage (~5%) for their ANN compared with a logistic regression model with regard to staging accuracy using several biopsy parameters including a number of positive cores, Gleason score sum, presence of Gleason Grade 4 or 5 tissue, total percentage of tumor involvement, and average percentage of tumor involvement per core as well as positive core and tumor location. A further study by Mattfeldt et al[14] also estimated the postoperative pathological stage of prostate cancer using ANN with preoperative parameters, which included age, histopathological variable, and prostate volume. Different ANN models could correctly predict pathological stages ≥pT3a in 90% of newly presented cases. However, the results of the above study were obtained from a small sample population ($n = 97$) in which case the methodology needs to be validated using a large cohort. Finally, one research group predicted pathological stage using seven parameters (age, PSA, clinical TNM classification, Gleason score, the percentage of tumor-positive biopsy cores, the maximum tumor length in biopsy cores, and PSA density).[15] The AUC of the ANN (0.825) was greater than for the logistic regression model (0.782) but was not statistical significant ($p = 0.69$). Recently, ANNs have helped clinics to discriminate the detection of prostate cancer in the daily routine and reduce unnecessary biopsies.[16]

The multivariate analysis of the logistic regression showed that not only PSA but also BMI took an independent risk factor for the prediction of the prostate cancer pathologic stage. Recent studies[17–19] have focused on the impact of obesity associated with prostate cancer progression, aggressiveness as well as clinically worse outcomes. Although obesity was not included in the parameters of previous referent ANN predictive models of prostate cancer, we nevertheless stressed its importance for the predictive accuracy of our model for differentiating ECE or OCD. Therefore, we added the obesity factor, assessed using the BMI value in the ANN and LR models, for predicting the prostate cancer pathologic stage.

Yoon et al[20] went as far as developing a Korean-based predictive model, which is a Korean Prostate Cancer Risk Calculator (KPCRC) to predict prostate cancer detection. The KPCRC improves the performance of the Prostate Risk Calculator 3 (PRC 3; a Dutch-based design) and PSA testing in predicting a Korean population's risk of prostate cancer. It implies that Asian populations require their own risk calculators to more accurately assess staging for prostate cancer. Bhojani et al[21] reported that the Partin Tables were not accurate enough to influence pre-operative decision making regarding the type or extent of RP. Although nomograms or Partin Tables have been developed and generally applied in Western populations, extrapolation of these results to oriental males may be of limited usefulness or validity.[4] Because serum PSA levels in Asian males are generally lower than those of Caucasian males of the same age, the clinical

significance of a given serum PSA value may differ between the two populations.[22] The appropriateness of the clinical application of Partin Tables in Asian populations to predict the pathologic stage of prostate cancer is therefore in doubt. Although the previous study of Matsui et al[15] validated the Partin Tables in a Japanese population, it had a weaker but not significant predictive ability than their ANN model, ($p = 0.54$). Nevertheless, this, to our knowledge, is the first clinical validation study of the Partin Tables in a Taiwanese population. Compared with the study reported by Poulakis et al[23] the ANN model incorporating MRI findings was significantly more accurate than LR and the Partin Tables for predicting the pathological stage of prostate cancer. As for our ANN model, when MRI findings were included in the input variables, the performance of the ANN showed a lower AUC and poorer discrimination power (data not presented). Therefore, MRI findings were omitted from the input variables of the final ANN model.

The limitations of our study include relatively small sample sizes, and the predictive accuracy of our model could potentially have been increased by incorporating new biomarkers. Kallikrein-2[24] and kallikrein-11 levels[25] were reported to improve the sensitivity and specificity of prostate cancer detection. Salami et al[26] stated that combining serum PSA, PCA3, and TMPRSS2:ERG in a multivariable algorithm optimized for clinical utility improved prostate cancer prediction. Other gene markers like prostate-specific membrane antigen, prostate stem cell antigen, apoptosis related molecules, and cell-cycle-related biomarkers could be designed and integrated into the ANN predictive model.[27] In the future, multi-center or multi-institute studies may therefore offer more insight into the optimization of the ANN model. Furthermore, other models, such as the Neuro–Fuzzy model, could be applied for more accurate clinical diagnoses.

In conclusion, the ANN model proved to be more accurate and had a larger AUC than LR, and validated the Partin Tables in predicting prostate cancer with OCD or ECE. ANNs can therefore be used to assist patients with newly diagnosed prostate cancer by helping to make more informed treatment decisions.

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