Aus der Klinik für Urologie
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DISSERTATION

Risk prediction models for biochemical recurrence after radical prostatectomy

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Contents

1. ABSTRACT

Introduction: Many computer models for predicting the risk of prostate cancer have been developed, including models for prediction of biochemical recurrence (BCR). However, models for individual BCR-free probability at individual time-points after a BCR-free period are rare.

Material and Methods: Follow-up data from 1575 patients who underwent laparoscopic radical prostatectomy (LRP) were used to develop an artificial neural network (ANN) to predict BCR and to compare it with a logistic regression (LR) model using clinical and pathologic parameters such as prostate-specific antigen (PSA). For individual BCR prediction at any given time after operation, additional ANN and LR models were calculated every 6 months for up to 7.5 years of follow-up.

Results: The areas under the receiver operating characteristic (ROC) curve (AUC) for the ANN (0.754) and LR models (0.755) calculated immediately following LRP were larger than those for Gleason Score (GS) (AUC: 0.715; P = 0.0015 and 0.001) or PSA (AUC: 0.619; P always <0.0001) alone. The GS predicted the BCR better than PSA (P = 0.0001), but there was no difference between the ANN and LR models (P = 0.39).

Conclusions: This study may enable a more accurate prediction of BCR. A patient who has undergone LRP should be able to use our curves to estimate his individual BCR-free probability. Our research fills the gaps for the prediction of an individual's BCR-free probability and in the application of ANNs for the prediction of BCR after LRP, thereby providing background for future investigations.

1. ABSTRAKT (Deutsch)

Einleitung: Viele Computermodelle zur Vorhersage des Risikos von Prostatakrebs sind entwickelt worden, einschließlich die zur Vorhersage eines biochemischen Rezidivs (BCR). Modelle zur individuellen Vorhersage eines BCR zu verschiedenen Zeitpunkten nach einer BCR freien Zeit sind jedoch selten.

Material und Methoden: Follow-up-Daten von 1575 Patienten, die eine laparoskopische radikale Prostatektomie (LRP) erhielten, wurden verwendet, um ein künstliches neuronales Netzwerk (ANN) zur Vorhersage eines BCR aufzubauen. Dieses wurde mit Modellen der logistischen Regression (LR) und mit klinischen und pathologischen Parametern wie dem prostataspezifischen Antigen (PSA) verglichen. Für eine individuelle BCR Vorhersage zu einem bestimmten Zeitpunkt nach der Operation wurden zusätzliche ANN- und LR-Modelle alle 6 Monate, bis zu 7,5 Jahren Follow-up berechnet.

Ergebnisse: Die Flächen unter den ROC-Kurven (engl. area under the curve, AUC) die für das ANN (0,754) und LR Modell (0,755) unmittelbar nach LRP errechnet wurden, waren größer als die für den Gleason Score (GS) (AUC: 0,715, P = 0,0015 und 0,001) und PSA (AUC: 0,619; P immer <0,0001) allein. Der GS prognostiziert ein BCR besser als PSA (P = 0,0001), aber es gab keinen Unterschied zwischen den ANN- und LR-Modellen (P = 0,39).

Zusammenfassung: Die Ergebnisse dieser Studie können eine genauere Vorhersage eines BCR ermöglichen. Ein Patient, der sich der LRP unterzogen hat, sollte unsere Kurven nutzen können, um seine individuelle BCR-freie Wahrscheinlichkeit einzuschätzen. Unsere Forschung füllt die Lücken in der Vorhersage einer individuellen BCR-freien Wahrscheinlichkeit und die Lücken in der Anwendung von ANNs zur Vorhersage der BCR nach LRP. Dieses sind Voraussetzungen für zukünftige Untersuchungen.

2. INTRODUCTION

2.1 Incidence trends and treatments for PCa

Over the last few years, the prevalence of prostate cancer (PCa) has risen significantly, and PCa is now one of the most common malignant tumors of men globally, ranked second in incidence and sixth in mortality.[1] In most countries, even low-incidence countries, the incidence of PCa is increasing. Patients with early PCa are usually asymptomatic upon presentation. By contrast, patients with advanced disease might present with urinary signs and symptoms or ostealgia. Patients with these manifestations of advanced disease have a poor prognosis. However, because of prostate-specific antigen (PSA) screening and improved treatments, the mortality rate of PCa is on a sustained downward trend.[2]

Beside active surveillance and radiation therapy, many patients with localized prostate cancer undergo open or laparoscopic radical prostatectomy (LRP). The elevated PSA level of patients should decrease in 2 to 4 weeks after the LRP to clinically undetectable levels. Patients with adverse pathology or advanced or metastatic disease receive other treatments, including radiotherapy, endocrine therapy, and chemotherapy.

2.2 Definition of BCR and the predictors of BCR

A PSA level that does not decrease clearly after radical prostatectomy indicates that the patient already had metastatic disease before surgery. An undetectable serum PSA level that gradually increases after LRP to 0.1 or 0.2 ng/mL is defined as biochemical recurrence (BCR).[3] This increase is usually considered to be a prognostic sign for the development of clinical recurrence and metastasis.[4] Clinical recurrence or metastasis will not occur without the prior development of BCR.[4] In addition, for patients whose PSA has dropped after LRP, the amount of time to appearance of BCR is clinically significant. A postoperative PSA level that increases rapidly from an undetectable level over a few weeks or months after LRP is also considered as a sign of metastatic disease. A PSA level that

decreases to an undetectable level and remains undetectable for 2 to 4 years after surgery before increasing may be evidence of local recurrence.[5] In patients with LRP that develop clinical recurrence or metastatic disease, the PSA level starts to increase 6 to 48 months before clinical symptoms may appear.[6] About 77.0%, 16.6%, 4.9%, and 1.5% of BCR patients develop BCR within 5 years, between 5 to 10 years, between 10 to 15 years, and longer than 15 years after LRP, respectively.[7] Therefore, early identification and treatment of BCR are very important for increasing a patient's probability of long-term survival.

The Gleason score (GS), preoperative PSA level, margin status, and pathological stage (pT) are currently the main parameters used for BCR prediction.[8] Chay and Smith[9] found that the best predictors of BCR at 5 years after LRP are margin positivity, GS ≥8, and seminal vesicle invasion, with the respective accuracies ranging from 50% to 70%, 55% to 95%, and 35% to 65%. A positive margin was the strongest risk factor for local recurrence, and seminal vesicle invasion was the strongest risk factor for metastasis and death. Babaian et al.[8] reported that the strongest prognostic factor for BCR was pT. The combination of pT with the Gleason score provides the greatest likelihood of identifying high-risk patients who require further treatments.

Some investigators have also evaluated the GS of biopsy tissue,[10] the clinical TNM stage,[10] preoperative prostate-specific antigen velocity,[11] PSA doubling time,[12] serum testosterone level,[13] and analysis of iconography data[14] as predictive factors. Several biomarkers, including heterochromatin protein 1 gamma,[15] vesicular monoamine transporter 2,[16] karyopherin alpha 2,[17] and prostate specific membrane antigen,[18] have also been found to be significantly associated with BCR.

2.3 Prediction models for PCa

Several multivariate programs, including logistic regression, linear or penalized discriminant analysis, support vector machines (SVMs), classification and regression trees, learning vector quantification, and artificial neural networks (ANNs) have been used for the diagnosis and evaluation of malignancies, including prostate cancer, during the last few

years; and some have been found to be helpful for estimating patient outcome. These programs have acted to provide support for clinical decision making and as powerful computational tools for categorizing patients. They identify matching patterns in datasets and forecast outcomes by evaluating a set of ‘inputs’ that contain patient-specific information such as serum PSA level, prostate volume, and percent free PSA (%fPSA). The methods increase the chance that the health of an individual patient will be reflected in the results generated by the program.

The diagnosis and prediction of a malignant disease traditionally were based on univariate factors such as individual biomarkers. However, unlike the traditional methods, the multivariate methods listed in the previous paragraph are believed to have improved the sensitivity, specificity, and accuracy of tumor diagnosis and classification, as well as the ability to estimate the prognosis of a patient with cancer.

ANNs are currently developing rapidly and are known to be ideal methods for diagnosing PCa. What exactly is an ANN? In a nutshell, it is an adaptive computational model. It aims to replicate the processes performed by interwoven brain neurons; an ANN learns from external and internal input data, changes its properties accordingly, and the correct results produced by an ANN reinforce the processes that led to those results.[19]

An ANN can reduce the need for both initial and repeat biopsies that are performed for the diagnosis of PCa. One of the biggest advantages of ANNs is that for any given sensitivity (e.g. 90% or 95%), an ANN can improve the specificity and decrease the false-positive rate of any parameter used for the diagnosis of PCa.[20-23]

The development of a model usually begins with the training or learning phase. Back-propagation networks are trained or learn using a dataset that contains both input and output data. Once the trained model is able to perform calculations with these inputs, it can take in a new input message, perform data analysis, assign weight to the data, and forecast the output. The output value ranges between 0 and 1, and indicates the chance of developing a specific disease. As a case in point, the decision to perform a prostate biopsy is largely made based on exceeding a defined threshold value, which relies on a predefined

value for sensitivity (or sometimes specificity). Therefore, if the cut-off value (at 95% sensitivity) is 0.3, then a value<0.3 will be interpreted as no indication for biopsy. However, if the calculated output value equals 0.5, a biopsy will be recommended. After the training phase, the model will be assessed or validated.

An external validation is needed to guarantee the authenticity of the model. In other words, the entire external validation process must be performed based on a single premise, which means all datasets must be independent of the training data. The following important parameters will be employed to assess a model's discriminatory power (distinguishing correctly between two classes): specificity, sensitivity, positive or negative predictive values, and the area under the receiver operating characteristic (ROC) curve (AUROC or AUC). The AUC curve graphically depicts the performance of a system.

The last step in the development of the model is the so-called calibration step, which uses a graphical tool to reveal the similarity of the predictions to the true probabilities. Detailed methodological descriptions of models,[24,25] ANNs,[26,27] comparisons of models,[31] and the limitations of these processes (including decision-curve analysis)[28] have been published elsewhere.[29]

Age, PSA, %fPSA, prostate health index (Phi), prostate volume, digital rectal examination (DRE) status, prostate cancer gene 3 (PCA3), TMPRSS2:ERG (T2:ERG) fusion gene, and prostate imaging findings have now all been adopted as markers for early detection, which can be entered into high-powered computational models to enable a more comprehensive diagnosis. These models have been found to provide improved sensitivity and accuracy.[30,31]

Most of the previous prediction models for prostate cancer are based on LR, and ANNs only make up a small proportion of the array of models available for prediction. Many LR models have been established for BCR prediction,[32] by contrast, only a few ANNs are available, and no ANN is available free online, and models that can predict outcomes at many time points after LRP have to date not been explored.[30] Our ANNs are particularly applicable for calculating a patient's risk of developing BCR at various time points after the

LRP.[33]

Many studies have found that ANNs have obvious advantages over the use of any single biomarker for the detection of PCa, including reduction in the number of unnecessary biopsies, better prediction of BCR or recurrence, and better estimation of the probability of survival.[23,34-38] In a relatively large study of 928 patients, Stephan et al. developed and tested an ANN with input data that included serum PSA, %fPSA, patient age, prostate volume, and DRE status, and found that it was superior to PSA.[39] The ANN evaluated patients stratified into groups with the following PSA ranges: 2-4 ng/mL, 4.1-10 ng/mL, and 10.1-20 ng/mL. At 90% sensitivity, the ANN performed better than PSA in all ranges, with increased specificities ranging from 32% to 44%.[39]

2.3.1 Working principles and development of ANNs

An ANN is usually divided into 3 parts: the input, hidden, and output layers (Fig. 1). During the training phase, by changing the weight coefficients and the threshold values, the ANN analyzes and weighs the input data, and “learns” the relationships between inputs (variables) and outputs (prediction results). Thereby it gradually reduces the number of prediction errors.

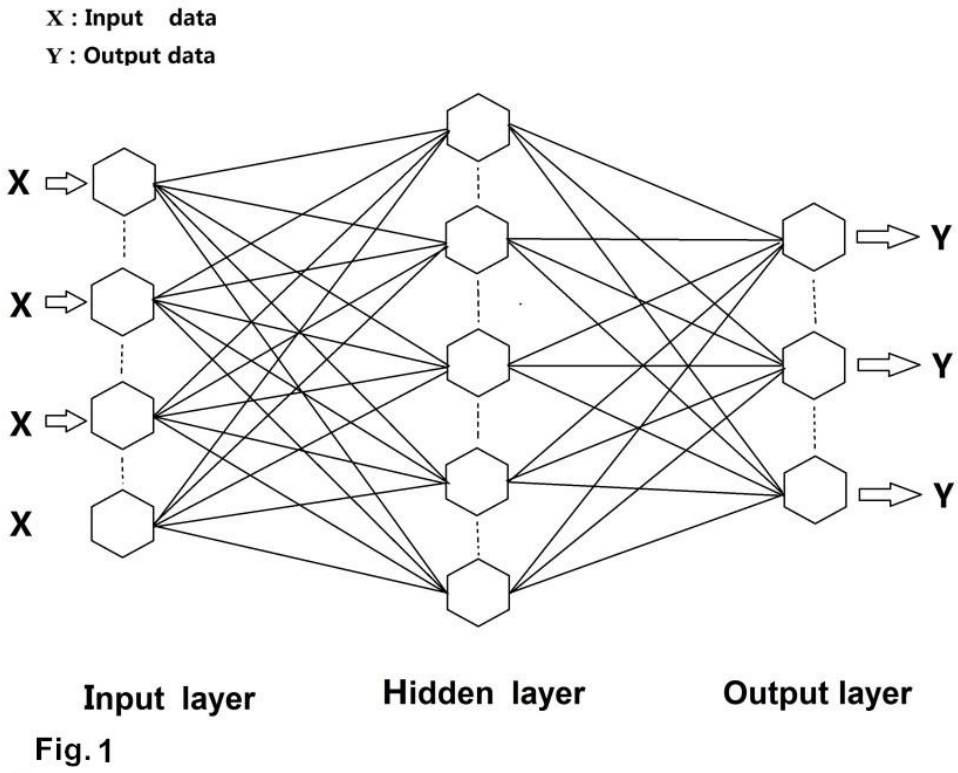


Fig. 1

McCulloch and Pitts[40] proposed the first back propagation model in 1948, Hebb[41] introduced the learning rules in 1949, and Rosenblatt[42] first introduced the clinical use of ANNs for radiology in 1958. Over 3 decades passed until Baxt[43] described and analyzed the working conditions of ANNs for the diagnosis of myocardial infarction. Increasing numbers of applications followed, with ANNs used for the diagnosis of diseases such as PCa, and breast and colorectal carcinoma and others.[44,45]

2.3.2 ANNs for detection and other aspects of PCa

This chapter summarizes the most important data on different ANNs applied to PCa, which were previously reviewed in detail by our group of investigators.[30] In 1994, Snow et al.[45] used first a neural network to predict the outcomes of prostate biopsy and the prognosis after radical prostatectomy for PCa. Finne et al.[20] found that at 95% sensitivity, their multilayer Perceptron ANN achieved not only better specificity than LR or %fPSA (respectively 33%, 24%, and 19%), but also higher forecast accuracy than LR ($p < 0.001$) in biopsies of 656 patients. As mentioned previously, an ANN that was developed by Stephan

et al.[39] to calculate an individual patient's risk of a positive prostate biopsy improved specificity by 32%-44% at 90% sensitivity over a range of PSA values.

The newly developed screening techniques combined with ANNs were found to lead to reduction in the large number of unnecessary biopsies. One study of 151 biopsied men revealed that 62.3% of prostate biopsies (71 of 114 men without cancer) would have been unnecessary if an ANN had been adopted. At 92% sensitivity, an ANN achieved a higher specificity than %fPSA (62% versus 11%, respectively) for detection of PCa.[46] Clinically, 49% of all biopsies in the study (74 out of 151) would have been unnecessary. A later study by our working group found that in groups of PCa patients stratified according to biopsies and PSA distribution, the ANN model established with only 2 variables, Phi and PCA3, obtained the largest AUC, compared with ANNs established with other variables.[31] In the repeat biopsy group, the ANN yielded an even better AUC (0.78) with the addition of a third variable, T2:ERG.[31]

For patients with PCa, an ANN can be used immediately after LRP to predict which patient belongs to the around 30% of patients who might develop recurrence.[47] One study showed that an ANN that used the GS, WHO grade, and maximum tumor diameter as variables predicted the outcome of 40 patients with pT2N0 PCa with an accuracy of 85%.[48] Benefited from the contribution of the morphometric features of prostate cancers, including the volume and surface area of the epithelial tumor component and of the lumina of the neoplastic glands per unit tissue volume, the same ANN predicted PCa progression with 93% accuracy.[48] Compared with other models (principal component analysis, decision-tree analysis, and stepwise logistic regression), an ANN gained the highest AUC (0.80) and had a sensitivity of 0.74, specificity of 0.78, positive predictive value (PPV) of 0.71, and negative predictive value (NPV) of 0.81.[49]

With respect to predicting the complications of radiotherapy, an ANN trained on clinical data was found to predict biochemical control and complications in the rectum or bladder. However, the sensitivity and specificity were only around 55%.[50] The sensitivity of another ANN could be increased if the input data were carefully classified, based on the degree of

severity of the complications in the bladder and rectum.[51] In contrast with support vector machines (SVMs) with an AUC of 0.7, an ANN with an AUC of 0.7 had higher accuracy.[51] Currently, only limited data have been used to build an ANN to evaluate the effects of radiotherapy, or the possibility of BCR after radiotherapy.[52,53]

As described in the previous paragraphs, a suitable ANN can reflect and predict the situation of BCR. In this study, we assessed the ability of ANN and LR models to predict BCR. We also analyzed ANN and LR models for assessing the risk of BCR every 6 months after LRP. This process provides a more precise estimate of BCR risk over any time period after surgery. ANN is considered to be a good option for not only the Cox models but also other regression models.[54] From a practical standpoint, considering an already elapsed recurrence-free interval, tools for estimating the probability of recurrence-free postoperative survival at certain time points are greatly needed.

3. MATERIALS AND METHODS

3.1 Patient Selection

According to the database of our institution, 1897 patients with PCa underwent LRP from 1999 to 2007. Among those patients, 322 were lost to follow-up or were excluded because of neo-adjuvant hormonal therapy. The remaining 1575 patients were divided into 2 separate groups: the non-BCR group consisting of 1300 patients (82.5%) and the BCR-group consisting of 275 patients (17.5%). The median follow-up period was 82.1 months (range 0.2 to 129.5 months).

3.2 Data collection

BCR was defined as serum PSA levels > 0.1 ng/mL at 2 successive time points. Prior to surgery, all of the blood samples were measured by Immulite® 2000 assays. The collected data included the following: age, PSA, %fPSA, pT, DRE status, prostate weight, margin status (positive surgical margin [PSM] or negative surgical margin [NSM]), and GS. Prostatectomy specimens were grouped according to the following pTs in order to assess the distributions of parameters: pT2, pT3/4; GS < 7, GS = 7, GS > 7; PSM or NSM; positive or negative DRE. PSA, margin status, pT, and GS were used for analyzing ANN and LR.

The study protocol was approved by an ethics committee and was performed under the guidelines of Diagnostic Accuracy.[55]

3.3 Statistical analysis

MATLAB-software and the Neural Network Toolbox (Mathworks, Natick, MA, USA) were used for ANN and LR computations. The ANN had three layers: input layer, hidden layer and output layer. The input layer of an ANN had four neurons, the hidden layer had two neurons, and the output layer had one neuron, which indicated the probability of non-BCR. Follow-up data was collected every 6 months after LRP. The data were used for

reference in each model, and these models (ANN and LR) were used to assess the status of the non-BCR patients remaining at each time of data collection and the uncensored patients, and excluding the patients who developed BCR earlier. The leave-one-out method was applied to all models for internal validation. SPSS 19.0 (IBM, Chicago, IL, USA) and MedCalc 12.4.0 (MedCalc Software, Mariakerke, Belgium) were used for all comparisons of variables. ROC curves of specificity and sensitivity were constructed, and AUCs were determined. ROC curves were compared using the method of Delong et al.[56] The prediction outcomes were analyzed by the Mann-Whitney U test for continuous variables and Fisher's exact test for ordinal variables. $P < 0.05$ was considered statistically significant.

4. RESULTS

4.1 Baseline characteristics

Table 1 shows the clinical characteristics of patients and the distribution of clinicopathololological parameters of the BCR and non-BCR patients. As seen in Table 1， none of the differences in the following parameters were significant for the two patient groups: age (P = 0.37), PSA (P = 0.12), %fPSA (P = 0.26), prostate volume (P = 0.33) and PSA density (P = 0.11). Differences in the GS (except for GS = 7, P = 0.12), margin status, and pT were significant.

Table 1. Clinical characteristics of the study population[a]

Characteristics	Total	Non-BCR	BCR	P
Number	1575	1300	275	
Age (yr)				0.374[b]
Median (IQR25%-75%)	63 (59-66)	63 (59-66)	63 (59-67)	
Range	43-75	43-75	43-75	
PSA (ng/mL)				0.115[b]
Median (IQR25%-75%)	7.5	7.5 (5.2-10.4)	7.5 (6.3-14.1)	
Range	1.3-50.7	1.3-50.7	1.7-50.6	
%fPSA				0.257[b]
Median (IQR25%-75%)	9.35	9.60 (6.67-13.4)	8.0 (6.07-11.6)	
Range	1.18-41.2	1.18-41.2	1.57-27.0	
PV (mL)				0.334[b]
Median (IQR25%-75%)	35 (26-47)	35 (26-48)	30 (25-42)	
Range	7-190	7-190	12-105	
PSA density(ng/mL/cc)				0.108[b]
Median (IQR25%-75%)	0.21	0.20 (0.13-0.31)	0.29 (0.18-0.44)	
Range	0.02-1.66	0.02-1.66	0.04-1.64	
DRE positive	548	410	138	< 0.0001[c]
R = 1	488	341	147	< 0.0001
Gleason score				< 0.0001
< 7 (%)	549 (35)	509 (39)	40 (15)	
= 7 (%)	766 (49)	644 (50)	122 (44)	
> 7 (%)	260 (16)	147 (11)	113 (41)	
pT (%)				< 0.0001
pT = 2 (%)	1119 (71)	1004 (77)	115 (42)	
pT = 3 (%)	446 (28)	292 (22)	154 (56)	
pT = 4 (%)	10 (1)	4 (1)	6 (2)	

IQR: interquartile range; BCR: biochemical recurrence; DRE: digital rectal examination; %fPSA: percent free PSA; PSA: prostate-specific antigen; PV: prostate volume; R1: margin status. a Values in parentheses are IQRs or percentages of numbers of patients in the group or Total; b Mann–Whitney U test; c Fisher's exact test

4.2 ROC analysis of selected parameters

According to the predicted results shown in Table 2, BCR specificities that were calculated by ANN and LR models using values of PSA, margin status, pT, and GS determined immediately after LRP, achieved peak specificities at both sensitivity cutoffs of 90% and 95%.

Table 2. ROC analysis with ANN and LR prediction results at 90% and 95% sensitivity

	90% Sensitivity		95% Sensitivity		AUC	95% CI [a]
	Spec	CI	Spec	CI		
ANN	35.1	32.6 - 37.8	20	17.9 - 22.3	0.754	0.721-0.786
LR	36.5	33.9-39.2	18.8	16.8-21.1	0.755	0.723-0.787
Gleason	n.a.		8.92	7.4-10.6	0.715	0.680-0.750
PSA	18.6	16.5-20.8	8.46	7.0-10.1	0.619	0.582-0.657

GS: Gleason score; ROC: receiver operating characteristic; ANN: artificial neural network; AUC: area under ROC curve; CI: confidence interval; LR: logistic regression; PSA, prostate-specific antigen. a 95% confidence interval of the respective AUC

Compared with ANN and LR, GS and PSA have lower specificities and AUCs. In Fig 2, the two models show larger AUCs than GS and PSA. Table 3 shows pairwise comparisons of prediction models with other parameters, prediction models with each other, and GS with PSA. As shown in Table 3, the difference between ANN and LR was not significant ($P = 0.39$); however, they achieved better predictions of BCR than PSA and GS ($P = 0.0015$ for ANN vs. GS; $P < 0.0001$ for ANN vs. PSA, LR vs. Gleason, and LR vs. PSA).

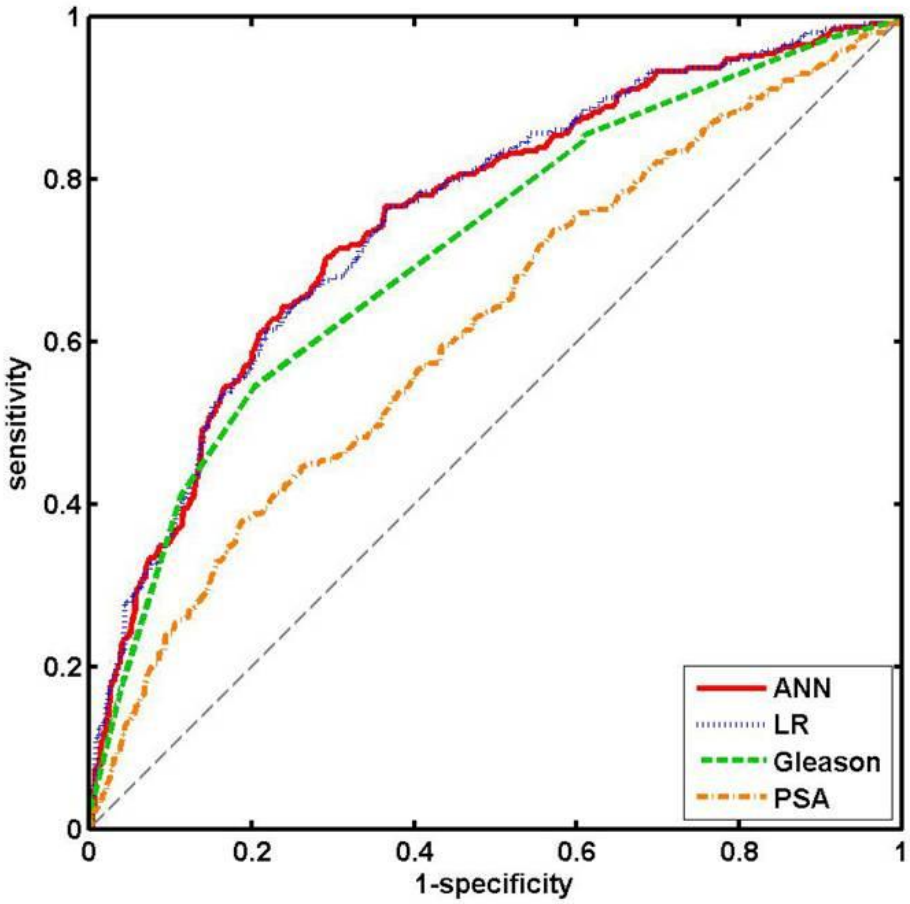


Fig. 2

Fig. 2 ROC curves for the models and variables: ANN (AUC 0.754), LR (AUC 0.755), Gleason score (AUC 0.715), and PSA (AUC 0.619).

Table 3. Pairwise comparison of prediction methods

Pairwise comparison of methods	ANN vs. LR	ANN vs. Gleason	ANN vs. PSA	LR vs. Gleason	LR vs. PSA	Gleason vs. PSA
AUC difference between areas	0.001	0.039	0.134	0.040	0.136	0.096
95% Cls	0.002 -0.005	0.014 -0.063	0.093 -0.175	0.016 -0.064	0.095 -0.177	0.048 -0.143
P [a]	0.39	0.0015	<0.0001	0.0001	< 0.0001	0.0001

[a]Delong test.

4.3 Biochemical recurrence-free survival (BCR-FS) curves.

Fig.3 shows probabilities of BCR-FS at 2.5, 5, and 7.5 years after LRP for GS and ANN output for each category. PCa patients with GS < 7 show the highest probability for BCR-FS, while patients with GS = 7 or GS > 7 (Fig. 3A-C) have lower probability. ANN and LR showed similar predictive power for BCR-FS (LR data not shown). To identify patients with more urgent need for adjuvant radiation (and hormonal) therapy, we subdivided all patients into two groups based on the value of the ANN output (≥ median and < median). The median was calculated from 1575 ANN output values, with reference to the prevalence of non-BCR. Fig. 3D-F reveals the differences between the two groups of patients within 2.5, 5, and 7.5 years.

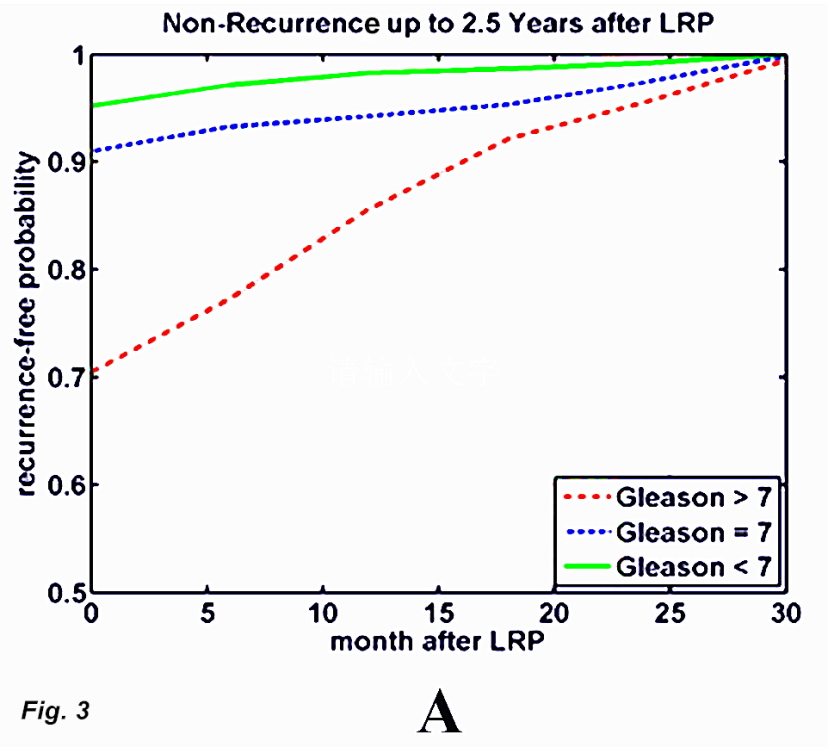

Non-Recurrence up to 2.5 Years after LRP
recurrence-free probability
month after LRP
Gleason > 7
Gleason = 7
Gleason < 7

Fig. 3 **A**

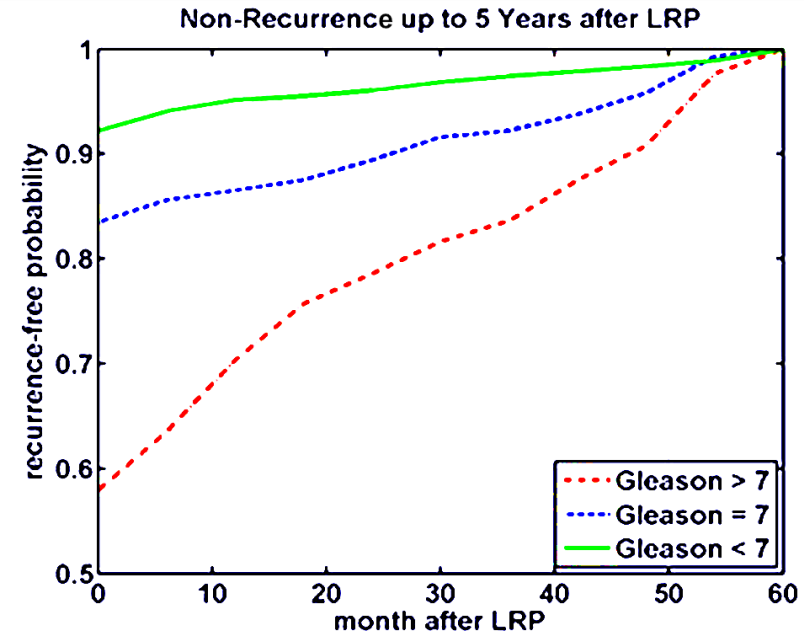

Non-Recurrence up to 5 Years after LRP
recurrence-free probability
month after LRP
Gleason > 7
Gleason = 7
Gleason < 7

Fig. 3 **B**

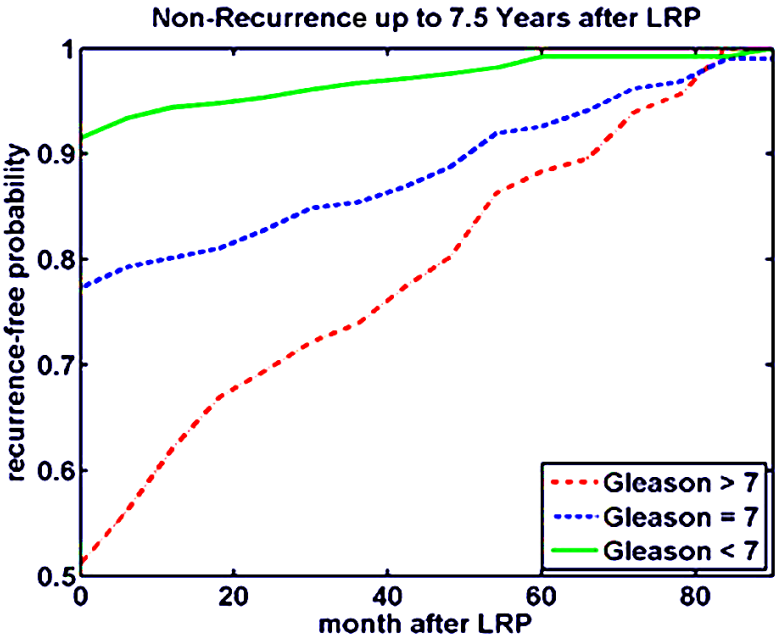

Non-Recurrence up to 7.5 Years after LRP
recurrence-free probability
month after LRP
Gleason > 7
Gleason = 7
Gleason < 7

Fig. 3 **C**

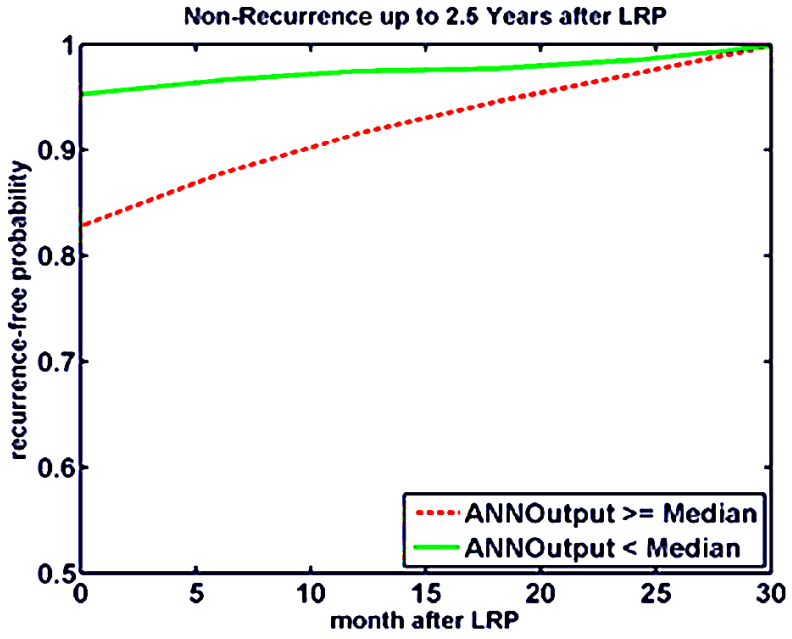
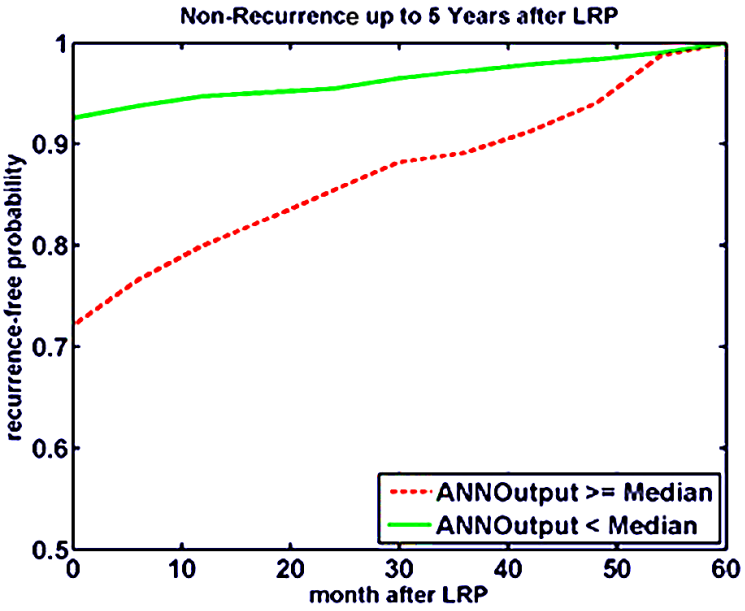
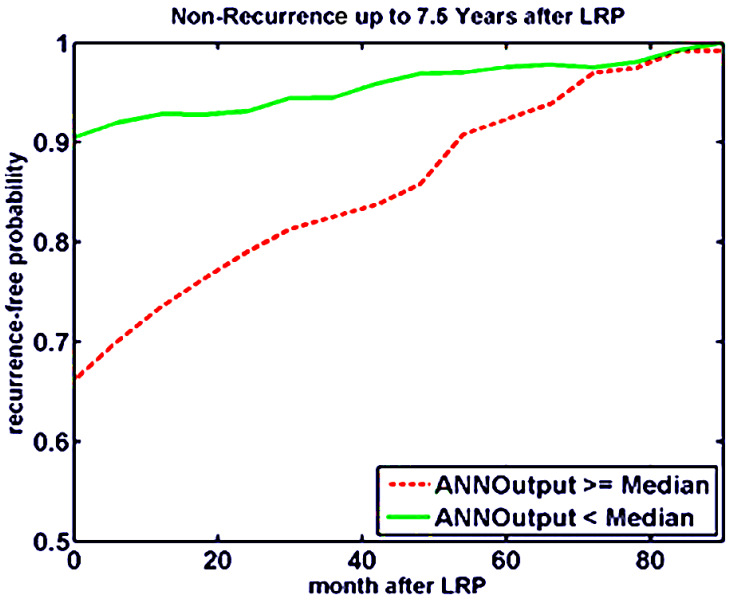

Non-Recurrence up to 2.5 Years after LRP
recurrence-free probability
month after LRP
ANNOutput >= Median
ANNOutput < Median

Fig. 3 **D**



E

Fig. 3



F

Fig. 3

Fig. 3. Probability of recurrence-free survival at 2.5, 5, and 7.5 years after LRP according to GS (A, B, C) and ANN output (D, E, F). The curves are based on Kaplan-Meier curves computed every 6 months after LRP for patients without BCR or for noncensored patients.

The analysis of individual ANN output values is not more accurate than GS alone for a patient with a GS < 7; however, for a GS ≥ 7, the prediction accuracy of ANN is improved. As shown in Table 4, 235 (23%) of 1026 PCa patients with GS ≥ 7 developed BCR. Of the 768 patients with an ANN output < median cutoff value, 127 (16.5%) developed BCR. Of the 258 patients with an ANN output ≥ median cutoff value, 108 (41.9%) developed BCR. Additional analysis of 260 patients with a GS of 8-10, showed that for an ANN output < median cutoff value, the proportion of patients who developed BCR declined from 43.5% (113 of 260) to 29.2% (28 of 96). It is notable that 51.8% of the patients with aggressive PCa and high ANN values developed BCR (85 of 164).

Table 4. Proportion of patients with BCR depending of GS and ANN output.

	All Patients	Patients with BCR	P[a]
GS 7 - 10	1026	235 (22.9 %)	
ANN output < cutoff	768	127 (16.5 %)	<0.0000
ANN output ≥ cutoff	258	108 (41.9 %)	
GS 8 - 10	260	113 (43.5 %)	
ANN output < cutoff	96	28 (29.2 %)	0.0006
ANN output ≥ cutoff	164	85 (51.8 %)	

[a]Calculated by Fisher's exact test.

5. DISCUSSION

Today, various types of ANNs are widely employed for the management of PCa. Variables such as PSA, prostate volume, and DRE are used as input parameters for the diagnosis of PCa.[23] ANN can aid in predicting the results of repeat prostate biopsies.[49] Although it can also assess the risk of lymph node metastasis in PCa patients,[38] an ANN is seldom used for BCR prediction.

Our data on BCR prediction show that ANN and LR models can identify significant relationships between variables and determine how the variables interact in the training set. Furthermore, these models estimate BCR more accurately than other variables for each individual patient with PCa.[57] Some studies have confirmed the capacity of ANN models to improve the prediction of outcome for PCa patients after prostatectomy.[45,49,58-60] The relevant data are shown in Table 5. One of the first studies in 1994 showed an accuracy of 87%.[45]

Table 5. Comparison of ANNs with different parameters

Study	No. of pat.	Variables	Sens. (%)	Spec. (%)	Accuracy (%)	AUC[a]
Tewari et al.[58]	1280	Age, PSA, systematic biopsy-based, stage, perineural infiltration, GS, duration of follow-up in months	76	85	76	0.831
Ziada et al.[37]	309	TNM stage, prostate size, PSA, GS, percentage of positive biopsies, age	79	81	80	
Potter et al.[60]	214	GS, extraprostatic extension, surgical margin status, age	88.2	61.1	74.3	0.713
Potter et al.[60]	214	DNA ploidy, the variance of 41 different nuclear morphometric descriptors	74.5	85.2	80.0	0.74
Potter et al.[60]	214	GS, extraprostatic extension, surgical margin status, age, DNA ploidy, QNG (the variance of 41 different nuclear morphometric descriptors)	84.3	72.2	78.1	0.735
Potter et al.[49]	196	Biopsy primary, secondary Gleason grade, biopsy Gleason sum, age, PSA	74	78	81	0.80
This study[33]	1575	Age, PSA ,GS	40.7	87.5	79.3	0.754

[a]AUC = area under receiver operating characteristic curve. QNG = quantitative nuclear grade

Although, the study by Tewari et al.[58] resulted in the best AUC value of 0.83, their accuracy was lower than in some of the other studies. Potter et al.[60] reached AUCs of 0.71, 0.74, 0.74, and 0.80 with different input parameters, but gained relatively lower specificity compared with our current study. Regardless of the varied levels of sensitivity and specificity, the ranges in accuracy (74% to 81%) and AUC (0.71 to 0.83) for all the studies are comparatively small. In other words, the input parameters were not conducive to improved BCR prediction.

Interestingly, %fPSA has been considered to be a useful marker in combination with PSA, DRE and biopsy findings to predict postoperative pathological stage and grade after prostatectomy;[61] however, in our study, %fPSA did not show differences in outcome. The median %fPSA values of the non-BCR and BCR patients were similar (9.6 vs. 8.0%; P = 0.26) (Table 1).

Our ANNs have an additional merit for patients with aggressive PCa (GS ≥ 7). According to our study, 235 of 1026 (23%) patients with GS values from 7 to 10 developed BCR. Of 768 patients whose ANN values were less than the chosen cutoff (median of ANN values), 16.5% developed BCR (Table 4). However, among the patients with an ANN value greater than the cutoff, 41.9% developed BCR, which is almost 2-fold of all patients who developed BCR (23%) regardless of the ANN output value, and nearly 3-fold the proportion of patients with an ANN output value less than the cutoff. However, since only 40 of the patients developed BCR, it can be concluded that analysis of individual ANN output values was not beneficial for patients with GS <7 PCa.

A further analysis of the 260 patients with a GS > 7 and with highly aggressive PCa revealed that the overall BCR rate decreased from 43.5% to 29.2% for patients with an ANN output value below the cutoff. In contrast, those patients with aggressive PCa and high ANN values had higher probability (51.8%; 85 of 164) of developing BCR. This individual risk estimation can be used to guide decision making for additional treatment, particularly for patients with high GS and ANN values.

Particularly, at every 6 months after surgery, our models can estimate the BCR-free

probability of a patient at specific time-points after a BCR-free period. For example, as shown in Figs. 3B and C, the probability of BCR in a patient with a GS = 7 and a recurrence-free period of 3 years after LRP is 8% up to 5 years and 14% up to 7.5 years. Without considering the 3 BCR-free years, the estimated risk for BCR would be ~22%. Compared with risk values estimated immediately after prostatectomy, our models provide a more optimistic prognosis.

This study has limitations. First, only internal validation results are available for all models. However, our aim was to determine the probability of improving BCR prediction for an individual patient at any time point after LRP. Second, the amount of available patient data decreased with increasing follow-up time.

PSA, GS, and patient age were significant markers for predicting the outcome of PCa.[4,62,63] These parameters, in addition to ANN output value, are currently the optimal choices for prediction of PCa recurrence. Furthermore, our ANN models enable prediction of BCR at an individual time point after LRP or for patients who have BCR-free timepoints. Other parameters such as %fPSA did not work as we had speculated. Although the %fPSA value is useful for the diagnosis of PCa, it is a relatively weak predictor of PCa and BCR. Therefore, it was excluded from our models.

6. CONCLUSION

Our ANN and LR models were substantially stronger predictors of BCR than the single traditional parameters GS and PSA. They aid in the estimation of the probability of an individual patient's BCR-free survival at any BCR-free timepoint after LRP. To improve the accuracy of BCR prediction, the GS can be combined with the ANN output value, which may enhance the precision of decision-making with regard to administering adjuvant therapy after prostatectomy, particularly for high-risk patients (GS ≥ 7).

7. LIST OF ABBREVIATIONS

%fPSA	free/total prostate specific antigen ratio
ANN	artificial neural network
AUC	area under the receiver operating characteristic
BCR	biochemical recurrence
DRE	digital rectal examination
fPSA	free PSA
GS	Gleason score
LR	logistic regression
RP	radical prostatectomy
NPV	negative predictive value
PCa	prostate cancer
PCA3	prostate cancer gene 3
Phi	prostate health index
pT	pathological stage
PPV	positive predictive value
ROC	receiver operating characteristic
SVMs	Support vector machines
T2:ERG	TMRPSS2-ERG
TMPRSS2	transmembraneprotease serine 2
tPSA	total PSA

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Eidesstattliche Versicherung Declaration in lieu of oath

„Ich, Xinhai Hu, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: [Risk prediction models for biochemical recurrence after radical prostatectomy] selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

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Datum Unterschrift

Anteilserklärung an etwaigen erfolgten Publikationen

Xinhai Hu hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Hu, X.H., Cammann, H., Meyer, H.A., Jung, K., Lu, H.B., Leva, N., Magheli, A., Stephan, C. & Busch, J. Risk prediction models for biochemical recurrence after radical prostatectomy using prostate-specific antigen and Gleason score. Asian J Androl 16, 897-901 (2014).

Xinhai Hu has contributed to literature review, the conception and design, research and analysis of data, discussions of content, the compare between artificial neural networks, logistic regression models and other parameters, the calculation of individual risk estimation and wrote the manuscript independently.

Publikation 2: Hu, X., Cammann, H., Meyer, H.A., Miller, K., Jung, K. & Stephan, C. Artificial neural networks and prostate cancer--tools for diagnosis and management. Nat Rev Urol 10, 174-182 (2013).

Xinhai Hu has contributed to literature review, the concept and design, screening out aspects of the wide applications of artificial neural networks, the collection of data, drafting the article independently.

Publikation 3: Stephan C, Rittenhouse H, Hu XH, Cammann H. Prostate-specific antigen (PSA) screening and new biomarkers for prostate cancer (PCa). eJIFCC 25, 55-130 (2014)

Xinhai Hu has contributed to discussions of PSA-screening, its development and effect assessment, the evaluation of PLCO screening trial, the compare with ERSPC screening, summary of effective marker, introduction of new found marker.

Publikation 4: Stephan, C., Jung, K., Semjonow, A., Schulze-Forster, K., Cammann, H., Hu, X., Meyer, H.A., Bogemann, M., Miller, K. & Friedersdorff, F. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. Clin Chem 59, 280-288 (2013)

Xinhai Hu has contributed to literature review, the conception and design, discussions of content, the compare between prostate cancer antigen 3, TMPRSS2:ERG gene fusion and prostate health index, the data analysis.

Unterschrift, Datum und Stempel des betreuenden Hochschullehrers/der betreuenden Hochschullehrerin

Unterschrift des Doktoranden/der Doktorandin

Curriculum vitae

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht

Publications

1. Hu, X.H., Cammann, H., Meyer, H.A., Jung, K., Lu, H.B., Leva, N., Magheli, A., Stephan, C. & Busch, J. Risk prediction models for biochemical recurrence after radical prostatectomy using prostate-specific antigen and Gleason score. *Asian J Androl* **16**, 897-901 (2014).

2. Hu, X., Cammann, H., Meyer, H.A., Miller, K., Jung, K. & Stephan, C. Artificial neural networks and prostate cancer--tools for diagnosis and management. *Nat Rev Urol* **10**, 174-182 (2013).

3. Stephan C, Rittenhouse H, Hu XH, Cammann H. Prostate-specific antigen (PSA) screening and new biomarkers for prostate cancer (PCa). *eJIFCC* **25**, 55-130 (2014).

4. Stephan, C., Jung, K., Semjonow, A., Schulze-Forster, K., Cammann, H., Hu, X., Meyer, H.A., Bogemann, M., Miller, K. & Friedersdorff, F. Comparative assessment of urinary prostate cancer antigen 3 and TMPRSS2:ERG gene fusion with the serum [-2]proprostate-specific antigen-based prostate health index for detection of prostate cancer. *Clin Chem* **59**, 280-288 (2013)

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