Asian Journal of Andrology (2014) 16, 897–901

www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Prostate Disease

Risk prediction models for biochemical recurrence after radical prostatectomy using prostate-specific antigen and Gleason score

Xin-Hai Hu[1], Henning Cammann[2], Hellmuth-A Meyer[1], Klaus Jung[1,3], Hong-Biao Lu[1,4], Natalia Leva[5], Ahmed Magheli[1], Carsten Stephan[1,3], Jonas Busch[1]

Many computer models for predicting the risk of prostate cancer have been developed including for prediction of biochemical recurrence (BCR). However, models for individual BCR free probability at individual time-points after a BCR free period are rare. Follow-up data from 1656 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, prostate-specific antigen (PSA), margin status (R0/1), pathological stage (pT), and Gleason Score (GS). 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. 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 that for GS (AUC: 0.715; *P* = 0.0015 and 0.001), pT 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). Our ANN and LR models predicted individual BCR risk from radical prostatectomy for up to 10 years postoperative. ANN and LR models equally and significantly improved the prediction of BCR compared with PSA and GS alone. When the GS and ANN output values are combined, a more accurate BCR prediction is possible, especially in high-risk patients with GS ≥7.

Asian Journal of Andrology (2014) **16**, 897–901; doi: 10.4103/1008-682X.129940; published online: 04 July 2014

Keywords: artificial neural network; prostate cancer; recurrence

INTRODUCTION

Prostate-specific antigen (PSA) is a widely accepted screening parameter for early detection of prostate cancer (PCa). Treatment of localized PCa is often performed by radical surgery such as laparoscopic radical prostatectomy (LRP).[1] The PSA value in most patients will drop to zero within 2 months after LRP. A consecutive increase of serum PSA up to 0.1 or 0.2 ng ml^{-1} is defined as biochemical recurrence (BCR).[2] BCR is considered a predictor of clinical recurrence and metastasis of PCa.[3,4] Therefore, early identification and treatment of BCR is important to improve the long-term survival.

Presently, Gleason Score (GS), preoperative PSA, and pathological stages (pTs) are the main parameters used to predict the risk of BCR.[5] For higher accuracy and specificity; multivariate logistic regression (LR) models such as nomograms[6] have been used to improve prediction. Most applications of LR in BCR prediction are available with standard nomograms, but there are only few artificial neural networks (ANNs) available for BCR prediction[7] and none is freely available online. Further, there are no available models that calculate the individual BCR free probability at multiple time-points after operation especially after different time periods without BCR.

Artificial neural networks imitate learning processes and interactions between human neurons.[8] During the training phase, it gradually reduces the deviation of prediction by learning the relationships among inputs (variables) and outputs (prediction results) as well as relationships between the input variables. Finally, the ANN has the ability to predict the probability of BCR.

Opinions vary regarding the comparison between ANN and LR.[9–14] Most criticism arises from the limited prediction accuracy due to limitations of the algorithm.[15,16] LR is a special form of ANN. If the relationships among input parameters are nonlinear, ANN models will perform better than LR. Otherwise, the LR is preferable because the influence of each parameter can be observed much easier than in ANNs.

In this study, we describe the suitability of ANNs as a prediction tools for BCR. Evaluation of the ability of a computer model to predict of BCR after radical prostatectomy is mainly based on the following parameters: the accuracy of the predicting models, the universality of the internal/external validation, correction capability, complexity, and clinical value.[17] Here, we analyzed ANN and LR performance in predicting BCR based on these criteria. In addition to the ANN and LR models immediately after surgery, we analyzed ANN and LR models that evaluate BCR risk at 6-month intervals, which allows for a more

[1]Department of Urology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [2]Institute of Medical Informatics, Charité - Universitätsmedizin Berlin, Berlin, Germany; [3]Berlin Institute for Urologic Research, Berlin, Germany; [4]Department of Urology, Changzhou No. 2 People's Hospital, Changzhou, China; [5]Stanford University School of Medicine, Stanford, CA, USA.
Correspondence: Dr. J Busch (jonas.busch@charite.de)
Received: 29 October 2013; Revised: 08 December 2013; Accepted: 22 January 2014

accurate prediction of BCR at any given time after surgery. ANN has already been described as a good alternative to Cox and other regression models.[18] From a practical point of view, there is an urgent need for tools that provide information on recurrence-free survival (FS) at distinct time points after radical prostatectomy taking into account the already elapsed recurrence-free interval.

MATERIALS AND METHODS

Study population

Between 1999 and 2007, 1897 PCa patients underwent LRP at our institution. Among them, 322 patients were lost to follow-up or had to be eliminated due to neo-adjuvant hormonal therapy or largely incomplete datasets. The remaining 1575 patients were divided into two groups: 1300 patients (82.5%) with no evidence of BCR (nonBCR) and 275 patients (17.5%) with BCR (BCR group). The median follow-up period was 82.1 months (range from 0.2 to 129.5).

Data collection

Biochemical recurrence was defined as serum PSA levels greater than 0.1 ng ml^{-1} at two consecutive time points. All preoperative blood samples were measured by Immulite® 2000 assays (Siemens Healthcare, Erlangen, Germany). Data collection included: age, PSA, free/total PSA (%fPSA), prostate weight, digital rectal examination (DRE) status, pT,[19] margin status (positive surgical margin [PSM] or negative surgical margin [NSM]) and GS.[20] For the parameter distribution analysis, pTs of the prostatectomy specimens were classified into pT2, pT3/4; GS <7, GS =7, GS >7; PSM or NSM; positive DRE or negative DRE. PSA, margin status, pT and GS were used for ANN and LR analysis.

This study was conducted under a local Ethics Committee approved protocol and obeys Reporting of Diagnostic Accuracy guidelines.[21]

Statistical analysis

Artificial neural network and LR models were computed using the MATLAB-software and the Neural Network Toolbox (Mathworks, Natick, MA, USA). Each ANN (feed forward network with error back propagation) had three layers: input layer with four neurons, hidden layer with two neurons and output layer with one neuron representing the nonBCR probability. Follow-up data after LRP were collected every 6 months and respectively added into the separate models. Every 6 months separate models (ANN and LR) were calculated with those patients still not having a BCR at this time-point (those with a BCR earlier were excluded) and those who were not censored. For all models, internal validation was performed with the leave one out method.

Statistical analysis was performed using SPSS 19.0 (IBM, Chicago, IL, USA) and MedCalc 12.4.0 (MedCalc Software, Mariakerke, Belgium) to compare all variables using receiver operating characteristic (ROC) analyses regarding sensitivity, specificity and areas under ROC curve (AUC). The comparison of ROC curves were performed with the method of Delong and the comparison of prediction results were conducted using Mann–Whitney *U* test for continuous variables and Fisher's exact test for ordinal variables. Differences were considered statistically significant if $P < 0.05$.

RESULTS

Baseline characteristics

Table 1 displays the patient characteristics as well as the distribution of clinico-pathological parameters of the BCR and nonBCR group. There were no relevant differences between the two groups for age ($P = 0.37$), PSA ($P = 0.12$), %fPSA ($P = 0.26$), prostate volume ($P = 0.33$), and PSA density ($P = 0.11$). In contrast, the pathological GS, margin status, and pT were different between the BCR and nonBCR group except for GS =7 ($P = 0.12$), as shown in **Table 1**.

Receiver operating characteristic analysis of selected parameters

Specificities of the BCR prediction results computed by ANN and LR models with the PSA, margin status, pT, and GS directly after LRP were the highest at both sensitivity cutoffs of 90% and 95%, as shown in **Table 2**. GS and PSA showed lower specificities and lower AUCs than ANN and LR. **Figure 1** clearly shows the larger AUCs of the two models compared with GS and PSA alone. **Table 3** displays the pairwise comparison of all parameters. While ANN and LR were not different ($P = 0.39$), ANN and LR predicted BCR better than PSA or

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

Characteristics	*Total*	*Non-BCR*	*BCR*	*P*
Number	1575	1300	275	
Age (year)				
Median (IQR 25%–75%)	63 (59–66)	63 (59–66)	63 (59–67)	0.374[b]
Range	43–75	43–75	43–75	
PSA (ng ml^{-1})				
Median (IQR 25%–75%)	7.5 (5.3–11.0)	7.5 (5.2–10.4)	7.5 (6.3–14.1)	0.115[b]
Range	1.3–50.7	1.3–50.7	1.7–50.6	
%fPSA				
Median (IQR 25%–75%)	9.35 (6.51–13.1)	9.60 (6.67–13.4)	8.0 (6.07–11.6)	0.257[b]
Range	1.18–41.2	1.18–41.2	1.57–27.0	
PV (ml)				
Median (IQR 25%–75%)	35 (26–47)	35 (26–48)	30 (25–42)	0.334[b]
Range	7–190	7–190	12–105	
PSA density				
Median (IQR 25%–75%)	0.21 (0.14–0.33)	0.20 (0.13–0.31)	0.29 (0.18–0.44)	0.108[b]
Range	0.02–1.66	0.02–1.66	0.04–1.64	
DRE positive	548	410	138	<0.0001[c]
R1=1	488	341	147	<0.0001[c]
Gleason, *n* (%)				
Gleason<7	549 (35)	509 (39)	40 (15)	<0.0001[c]
Gleason=7	766 (49)	644 (50)	122 (44)	
Gleason>7	260 (16)	147 (11)	113 (41)	
pT, *n* (%)				
pT=2	1119 (71)	1004 (77)	115 (42)	<0.0001[c]
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 patients' number; [b]Mann–Whitney U test; [c]Fisher's exact test

Table 2: ROC analysis with prediction results at 90% sensitivity and 95% sensitivity

	90% sensitivity		*95% sensitivity*		*AUC*	*95% CI[a]*
	Specificity	*CI*	*Specificity*	*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
GS	NA		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% CI of the respective AUC

GS ($P = 0.0015$ for ANN *vs* GS and $P < 0.0001$ for ANN *vs* PSA, LR *vs* GS and *vs* PSA, respectively).

Biochemical recurrence-free survival curves

Figure 2 displays probabilities for BCR-FS up to 2.5, 5, and 7.5 years after LRP for different categories of GS and ANN outputs. PCa patients with GS <7 always have the highest probability for BCR-FS compared with patients with GS =7 or GS >7 (**Figure 2a–2c**).

In predicting BCR-FS, ANN, and LR perform similarly (LR data not shown). To allow better differentiation of patients who more urgently may need adjuvant radiation (and hormonal treatment) we subdivided all patients using the continuous ANN output values and separated them into two groups below and above the median. This median output was calculated from the 1575 ANN output values according to the prevalence of nonBCR. **Figure 2d–2f** shows the difference between patients above and below the median ANN output values with up to 2.5, 5, and 7.5 years of follow-up.

Analysis of individual ANN output values had no benefit in patients with a GS <7 PCa but it improved the prediction for all patients with GS ≥7. Of all 1026 PCa patients with GS ≥7, 235 (23%) had a BCR (**Table 4**). Of the 768 patients with an ANN value below the median cutoff, only 16.5% ($n = 127$) developed BCR. On the other hand, of the 258 patients with an ANN value above the median cutoff, 41.9% ($n = 108$) developed BCR. Further analysis of the 260 patients with a GS >7 showed an overall BCR rate of 43.5% (113 of 260) that dropped tremendously when the ANN value was below the cutoff. Only 28 of 96 patients (29.2%) had a BCR. Interestingly, among patients with aggressive PCa and high ANN values, 51.8% had a BCR (85 of 164).

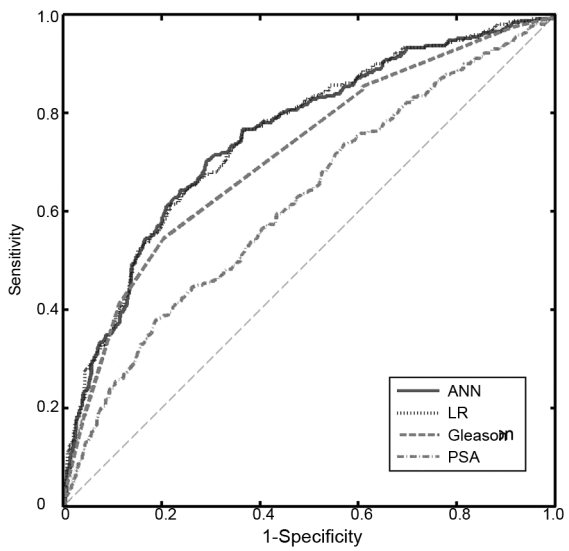

Figure 1: Receiver operating characteristic curves for the models: artificial neural network (area under ROC curve [AUC] 0.754) and logistic regression (AUC 0.755) and the variables Gleason Score (AUC 0.715) and prostate-specific antigen (AUC 0.619).

DISCUSSION

Different types of ANNs have been used for a variety of purposes in management of PCa. For example, PSA, prostate volume, DRE, and other variables are used as input parameters for diagnosing PCa.[22] ANN is also used to predict the outcome of repeat prostate biopsies,[23] and furthermore, to predict the risk of lymph node metastasis in PCa patients.[24] However, ANN applications to predict BCR are rare.[7,10]

Our data on BCR prediction show that ANN and LR models including the parameters PSA, margin status, pT and GS, can correctly simulate and reflect interactions between variables in the training set. The models improve the prediction better than any single variable and thus estimate BCR more accurately for each individual patient with PCa.[25] Some studies have verified that ANN models have the ability to improve prognosis prediction for PCa patients after prostatectomy.[7,10,26–29] These data have been summarized in **Table 5**. One of the first studies in 1994 demonstrated 87% accuracy.[26]

Among all available studies to date, the results by Tewari *et al.*[7] showed the best AUC with 0.83; however, their accuracy was somewhat lower than in the present study and in other studies. Potter *et al.*[26] gained similar AUCs of 0.71, 0.74, 0.74 using different input parameters, but the specificity was relatively lower than in our present study. However, despite large differences in sensitivity and specificity levels there are relatively small accuracy ranges (70%–87%) and AUCs between 0.71 and 0.83 for all studies. This demonstrates that the parameters that were used do not allow a better prediction of BCR. Interestingly, PSA has been thought to improve prediction of BCR following PCa diagnosis;[30] however in our study, %fPSA did not improve prognosis. The median values were not different between the non-BCR and BCR group (10.7 *vs* 9.2%; $P = 0.26$) (**Table 1**).

An important finding was the additional benefit of our ANN for patients with aggressive PCa (GS ≥7). Among 1026 patients, 235 had a BCR (23%). Patients with a low ANN value (below the chosen cutoff) had only 16.5% of the 768 BCR (**Table 4**). But if patients had an ANN value above the cutoff, 41.9% showed BCR. This rate is almost doubled in comparison to the 23% without considering the ANN output value and almost tripled in comparison to the group below the cutoff. However, analysis of individual ANN output values had no benefit in patients with GS <7 PCa, where only 40 patients had a BCR.

When further analyzing the 260 patients with highly aggressive PCa and a GS > 7, the overall BCR rate of 43.5% (113 of 260). This rate dropped when the ANN value was below the cutoff. Only 28 of 96 patients (29.2%) had a BCR. In contrast, those patients with aggressive PCa and high ANN values had a >50% likelihood to have a BCR (51.8%; 85 of 164). This individual risk estimation could support further treatment, especially in patients with high GS and high ANN values compared with lower risk patients.

Uniquely, our calculated models at every 6 months following surgery can provide the individual BCR free probability at individual

Table 3: Pairwise comparison of prediction methods

Pairwise comparisons methods	*ANN versus LR*	*ANN versus Gleason*	*ANN versus PSA*	*LR versus Gleason*	*LR versus PSA*	*Gleason versus PSA*
AUC difference between areas	0.001	0.039	0.134	0.040	0.136	0.096
95% CIs	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

ROC: receiver operating characteristic; CI: confidence interval; ANN: artificial neural network; AUC: area under ROC curve; LR: logistic regression; PSA: prostate-specific antigen; [a]Delong test

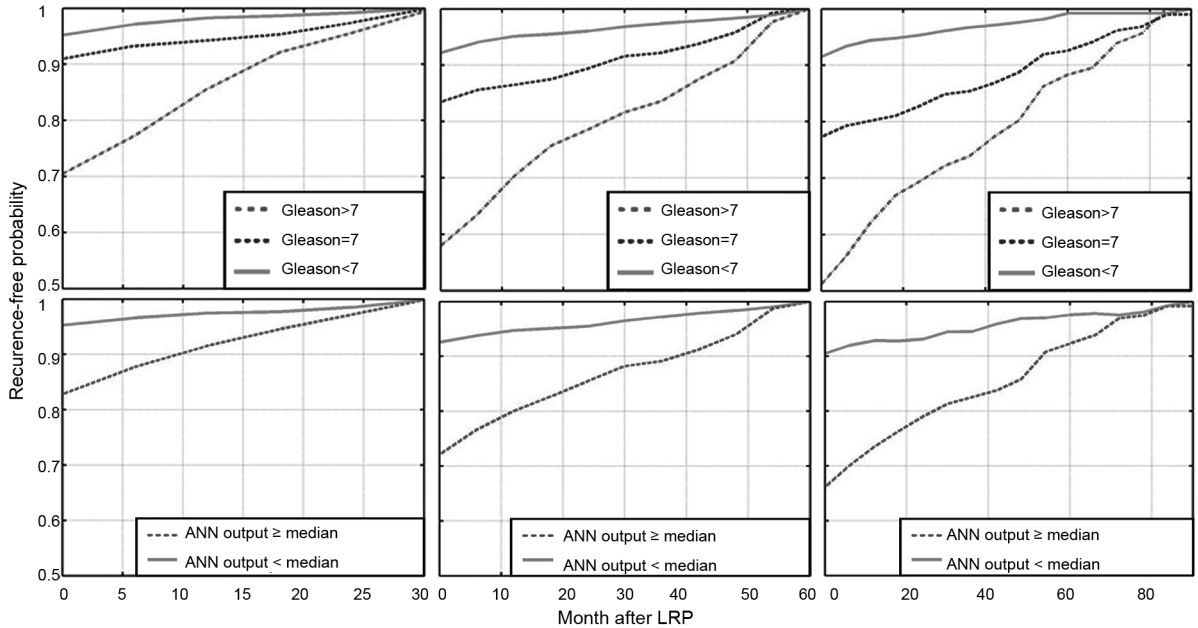

Figure 2: Probability of recurrence-free survival at 2.5, 5, and 7.5 years after laparoscopic radical prostatectomy (LRP) according to Gleason score (above three figures) and artificial neural network output (below three figures). The curves are based on Kaplan–Meier curves computed every 6 months after LRP for patients which are under investigation, that is, patients without biochemical recurrence or not censored patients.

Table 4: Proportion of patients with biochemical recurrence depending of Gleason score and artificial neural network output

	No. patients (n)	*Patients with BCR (n, %)*	*P*[a]
GS 7–10	1026	235 (22.9)	
ANN output<cutoff	768	127 (16.5)	<0.00001
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)	

ANN: artificial neural network; BCR: biochemical recurrence; GS: Gleason score.
[a]Calculated by Fisher's exact test

Table 5: Comparison of ANNs with different parameters

Study	*No. of patients*	*Variables*	*Sensitivity (%)*	*Specificity (%)*	*Accuracy (%)*	*AUC*
Tewari *et al.* [7]	1280	Age, PSA, systematic biopsy-based, stage, perineural infiltration, GS, duration of follow-up in months	76	85	76	0.831
Ziada *et al.* [29]	309	TNM stage, prostate size, PSA, GS, percentage of positive biopsy, age	79	81	80	
Potter *et al.* [26]	214	GS, extraprostatic extension, surgical margin status, age	88.2	61.1	74.3	0.713
Potter *et al.* [26]	214	DNA ploidy, the variance of 41 different nuclear morphometric descriptors	74.5	85.2	80.0	0.74
Potter *et al.* [26]	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
Porter *et al.* [28]	196	Biopsy primary, secondary Gleason grade, biopsy GS, age, PSA	74	78	81	0.80
Present study	1575	Age, PSA, GS	40.7	87.5	79.3	0.754

ROC: receiver operating characteristic; ANN: artificial neural network; AUC: area under ROC curve; GS: Gleason score; LR: logistic regression; PSA: prostate-specific antigen; QNG: quantitative nuclear grade, TNM: tumor, node, metastases, DNA: deoxyribonucleic acid

time-points after a BCR free period. For example, as shown in **Figure 2b**, a patient with a GS of 7 and a recurrence free survival of 3 years after LRP only has an 8% likelihood of a BCR up to 5 years, and 14% up to 7.5 years (**Figure 2c**). Without considering the three BCR free years, the estimated BCR risk would be ~22%. This allows for a more optimistic prognosis in comparison to those values calculating risk only immediately after prostatectomy.

A limitation of this study is the availability of only internal validation results for all models. However, our aim was to demonstrate the possibility of improving individual BCR estimation at any point after LRP. Another limitation was the decreased available patient data with increased follow-up time.

Nevertheless, patient's age, PSA, and GS were found to play a distinct role in PCa prognosis.[3,31,32] Currently, those prediction parameters and the ANN output value best predict a PCa recurrence. Further, with our ANN models, this prediction can be made for an individual time point after LRP and with patients who have BCR free time-points. Other parameters such as %fPSA or the margin status did not contribute as speculated before. The %fPSA performs well in PCa diagnosis, but is less competitive in the prognosis of PCa or BCR, therefore it is not used in our models.

CONCLUSION

The predictive ability of our ANN and LR models is better than single standard parameters GS and PSA. Our models for individual BCR free probability at individual time-points after a BCR free period offer an individual BCR prediction. By combining the GS and ANN output value, a BCR prediction is more accurate and may lead to a more accurate application of adjuvant therapy after prostatectomy especially in high-risk patients with GS ≥7.

AUTHOR CONTRIBUTIONS

CS, JB, HC, HAM, and KJ took part in conception and design, in acquisition, analysis, and interpretation of data. XHH and HBL took part in acquisition, analysis, and interpretation of data. NL and AM took part in the acquisition of data. All authors took part in drafting and revising the manuscript. All authors read and approved the final version of the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ACKNOWLEDGMENTS

This study was supported by a grant of the Berliner Sparkassenstiftung Medizin (Grant No. 89838600).

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How to cite this article: Hu XH, Cammann H, Meyer HA, Jung K, Lu HB, Leva N, Magheli A, Stephan C, Busch J. Risk prediction models for biochemical recurrence after radical prostatectomy using PSA and Gleason score. *Asian J Androl* 04 July 2014. doi: 10.4103/1008-682X.129940. [Epub ahead of print]