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Machine learning algorithms can more efficiently predict biochemical recurrence after robot-assisted radical prostatectomy

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Abstract

Objectives: To develop a model for predicting biochemical recurrence (BCR) in patients with long follow-up periods using clinical parameters and the machine learning (ML) methods.

Materials Method: Patients who underwent robot-assisted radical prostatectomy between January 2014 and December 2019 were retrospectively reviewed. Patients who did not have BCR were assigned to Group 1, while those diagnosed with BCR were assigned to Group 2. The patient's demographic data, preoperative and postoperative parameters were all recorded in the database. Three different ML algorithms were employed: random forest, K-nearest neighbour, and logistic regression.

Results: Three hundred and sixty-eight patients were included in this study. Among these patients, 295 (80.1%) did not have BCR (Group 1), while 73 (19.8%) had BCR (Group 2). The mean duration of follow-up and duration until the diagnosis of BCR was calculated as 35.2 ± 16.7 and 11.5 ± 11.3 months, respectively. The multivariate analysis revealed that NLR, PSAd, risk classification, PIRADS score, T stage, presence or absence of positive surgical margin, and seminal vesicle invasion were predictive for BCR. Classic Cox regression analysis had an area under the curve (AUC) of 0.915 with a sensitivity and specificity of 90.6% and 79.8%. The AUCs for receiver-operating characteristic curves for random forest, K nearest neighbour, and logistic regression were 0.95, 0.93, and 0.93, respectively. All ML models outperformed the conventional statistical regression model in the prediction of BCR after prostatectomy.

Conclusion: The construction of more reliable and potent models will provide the clinicians and patients with advantages such as more accurate risk classification, prognosis estimation, early intervention, avoidance of unnecessary treatments, relatively lower morbidity and mortality. The ML methods are cheap, and their powers increase with increasing data input; we believe that their clinical use will increase over time.

KEYWORDS
artificial intelligence, biochemical recurrence, machine learning, prostatectomy, prostate cancer, robot assisted

1 | INTRODUCTION

The introduction of computers to our daily life and the recording of electronic medical data led to the accumulation of a great deal of knowledge. These data are used during clinical practice, and modern medicine is developed accordingly. The machine learning (ML) method, which was developed based on statistics, computer sciences, and artificial intelligence (AI), facilitates the construction of new and more convenient algorithms by relieving more complicated relationships and relationship patterns that cannot be otherwise revealed by traditional statistical methods from large databases.[1,2]

Prostate cancer (PCa) is the most frequently diagnosed cancer among noncutaneous malignancies.[3] In the United States, 230.000 new PCa cases and 30.000 PCa-related deaths are detected annually. It is the 2nd most common cause of cancer-associated mortality in the male patient population.[3] It was reported that biochemical recurrence (BCR), which was associated with distant metastasis and cancer-specific mortality, was diagnosed in as high as 27% of the PCa patients who underwent radical prostatectomy (RP).[4–6] Two-third of these recurrences occurred during the initial 2-year period after surgery.[4–6] There is evidence suggesting that early identification of the patients with high risk for BCR and early diagnosis and treatment of BCR leads to individualization of patient management strategies, better oncological outcomes, and better estimation of prognosis.[7,8] Also, identifying the patients who have a low risk for BCR is essential for protecting the patients for avoiding the side effects of unnecessary treatments.[7,8]

Cancer of the Prostate Risk Assessment (CAPRA score), Kattan nomogram, and Han tables were the models developed to estimate BCR, and they became popular in clinical practice.[5,9–11] The predictive power of these models was increased by introducing multiparametric magnetic resonance imaging (mpMRI).[10,11] Recently, Wong et al.[2] compared the successes of classical Cox regression analysis and ML models in predicting early BCR after robot-assisted radical prostatectomy (RARP). In this study, we aimed to develop a model for predicting BCR in patients with long follow-up periods using clinical parameters and the ML methods.

2 | MATERIALS AND METHODS

2.1 | Patient cohort

This study was approved by the Ethical Review Committee of Bakirkoy Dr. Sadi Konuk Training and Research Hospital (2020/475). Data of the patients who underwent RARP in the same hospital's urology department between January 2014 and December 2019 were retrospectively reviewed.

Patients with a history of chemotherapy, radiotherapy, autoimmune disease, patients on steroids, and those who had viral or bacterial infections during the preoperative assessment were excluded. Patients who were preoperatively given radiotherapy or hormonotherapy for PCa, patients who did not undergo mpMRI or underwent mpMRI at another center, and patients who had distant metastasis or suspicion for distant metastasis were also omitted. Patients with a postoperative follow-up period of shorter than 12 months, patients with incomplete follow-up data, or those who received adjuvant radiotherapy were excluded.

All patients underwent RARP at least six weeks after the last transrectal ultrasound-guided (TRUS-guided) biopsy procedure. Preoperative blood tests were done two weeks before the surgery. Patients were classified as per risk stratification, and those with intermediate and high risk were screened for potential metastases by abdominopelvic computerized tomography and whole-body bone scan.[12] All mpMRI procedures were performed by 3 Tesla MRI Scanner (Magnetom Verio; Siemens). The PI-RADS (Prostate Imaging-Reporting and Data System) scores were determined based on the second version of PI-RADS (i.e., PI-RADS v2) reported by the American College of Radiology.[13] A prostate mpMRI result was regarded as positive if there were lesions with a PI-RADS v2 score of ≥2. Prostate volume (PV) was calculated by TRUS using the ellipsoid formula ($PV = height \times width \times length \times 0.52$) on axial T2WI images. The lesion with the highest PIRADSv2 score and the largest diameter was defined as an index lesion. The parameters regarding imaging were retrieved from mpMRI reports. The surgeries were performed by da Vinci SI or XI surgical systems® (Intuitive Surgical Inc.) using the Frankfurt technique described by Wolfram et al.[14] Bilateral nerve-sparing approaches were implemented in patients with preoperative potency who did not have extraprostatic spread according to mpMRI findings. Robot-assisted pelvic lymph node dissection was performed in patients who had a nodal metastasis risk of higher than 5%, according to Partin nomogram.[15]

The serum prostate-specific antigen (PSA) levels of the patients were checked 1 month after RARP. These assessments were repeated every 3 months during the first 2 years postoperatively and every 6 months afterward. Patients who did not have BCR were assigned to Group 1, while those diagnosed with BCR were assigned to Group 2.

2.2 | Data collection

Patient's demographic data, preoperative and postoperative parameters were all recorded in the database. Neutrophil-lymphocyte

ratio (NLR), platelet-lymphocyte ratio (PLR), and monocyte-lymphocyte ratio (MLR) were calculated by dividing the absolute neutrophil count (NC), platelet count (PC), and monocyte count (MC) to absolute lymphocyte count (LC), respectively. PSA density (PSAd) was calculated by dividing the serum total PSA level by PV. The De Ritis ratio was calculated by dividing the serum aspartate aminotransferase level to serum alanine aminotransferase level.[16]

All TRUS-guided prostate biopsy specimens were histopathologically reviewed according to the Gleason scoring system, while the clinical and pathological staging of the patients was done as per the 2009 tumor-node-metastasis (TNM) classification.[17] Patients were categorized as per National Comprehensive Cancer Network guidelines as low, middle, and high risk.[12] A positive surgical margin (PSM) was defined as the presence of a tumor at the inked margin. The BCR was defined as a postoperative serum PSA level of above 0.2 ng/ml in two consecutive measurements. Upgrading was defined as an increase in Gleason scores detected when biopsy and RARP specimen Gleason scores were compared. A biopsy specimen Gleason score of 3 + 4 and RARP specimen Gleason score of 4 + 3 was also regarded as upgrading.

2.3 | Statistical methods

Categorical data were given as numbers and percentages. Means and *SD*s were calculated for continuous variables. The normal distribution of the continuous variables was tested by the Shapiro-Wilk test. Means of two normally distributed groups were compared using Student's *t* test. Mann-Whitney *U* test was used for comparison of the means between non-normally distributed groups. Means of more than two normally distributed and non-normally distributed groups were compared by ANOVA and Kruskal-Wallis tests, respectively. The frequency of categorical variables was compared using Pearson χ^2 and Fisher's exact tests. The *p* values of <.05 were regarded as statistically significant. Univariable and multivariable binary logistic regression analyses were used to identify the predictive factors of BCR and develop a novel predictive model. The receiver operating curve analysis was performed to measure the model's predictive power. Statistical analysis was performed using Statistical Package of Social Sciences version 21 (IBM SPSS Statistics; IBM Corp.).

2.4 | ML models

We used Python 3.6.1 programming language and Scikit-learn 0.23.2 to train, evaluate, and test ML models. Three different ML algorithms were employed according to software engineers suggestions: random forest, K-nearest neighbour, and logistic regression. Random forest is an ensemble learning algorithm based on decision trees. In random forest, multiple decision trees with a different subset of features give a prediction, and the final prediction is based on the majority of those classifiers. The K-nearest neighbour algorithm searches for the nearest neighbors of samples and indicates the classes of those samples. Logistic regression models the probabilities for classification problems with two possible outcomes. A logistic regression classifier is a modified version of linear regression for classification. It uses the sigmoid function to classify samples. We split the data set into two parts: development set ($n = 324$) and test set ($n = 44$) rather than splitting the development set into train and validation set. Tenfold cross-validation was applied. We evaluated the accuracy of each model's probability output in the cross-validation and calculated the average of outputs to obtain a final output.

3 | RESULTS

3.1 | Patient characteristics

Data of 1019 patients who underwent RARP within the study period due to PCa were reviewed. After the application of inclusion and exclusion criteria, 368 patients were included in this study. Among these patients, 295 (80.1%) did not have BCR (Group 1), while 73 (19.8%) had BCR (Group 2). Comparison of these groups concerning 37 parameters, including demographic data and preoperative and postoperative laboratory work-up, histopathological evaluation, and imaging results are shown in Table 1. There was no significant difference between the two groups regarding blood group and Rh typing, American Society of Anesthesia scores, NC, LC, PC, PLR, MC, MLR ve De Ritis ratios. The mean duration of follow-up and duration until the diagnosis of BCR was calculated as 35.2 ± 16.7 and 11.5 ± 11.3 months, respectively.

3.2 | Results of univariate and multivariate analyses

The multivariate analysis revealed that NLR, PSAd, risk classification, PIRADS score, T stage, presence or absence of PSM, and seminal vesicle invasion were predictive for BCR. Results of univariate and multivariate analyses are altogether shown in Table 2. Classic Cox regression analysis had an area under the curve (AUC) of 0.915 with a sensitivity and specificity of 90.6% and 79.8% (Table 3 and Figure 1).

3.3 | ML models

Three different ML algorithms (i.e., random forest, K-nearest neighbour, and logistic regression) were tried to predict BCR. Thirty-seven parameters were used for creating a model. The predictive powers of all models are displayed in Table 3. Accuracy prediction scores for random forest, logistic regression, and K-nearest neighbour were 0.86, 0.83, and 0.86, respectively. The AUCs for receiver-operating characteristic curves were 0.95, 0.93, and 0.93, respectively

TABLE 1 Demographic data, characteristics, and clinical variables

No. patients (mean ± *SD*)	Total (*n*), 368	Non-BCR (*n*; %), 295 (80.1)	BCR (*n*; %), 73 (19.8)	*p*
Age (year)	62.3 ± 6	62.1 ± 5.9	63.3 ± 6.1	.121*
BMI (kg/m^2)	26.4 ± 2.4	26.5 ± 2.5	26.2 ± 2.1	.715#
NLR	2.2 ± 1.1	2.1 ± 0.9	2.6 ± 1.7	**.002**#
PSA (ng/dl)	10.3 ± 8.5	9.3 ± 7	14.3 ± 12	**<.001**#
PSAd	0.2 ± 0.2	0.2 ± 0.2	0.3 ± 0.2	**<.001**
PV (cc)	46 ± 19.2	46.4 ± 19.1	44.5 ± 20.1	.452*
mpMRI				
PV	45.3 ± 20.9	45.4 ± 20.1	45 ± 24.1	.898*
PIRADS, *n* (%)				
3	52 (14.1)	47 (21.5)	7 (10.9)	**<.001**#
4	164 (44.6)	137 (62.6)	27 (42.2)	**3 vs 5 < 0.001**
5	65 (17.7)	35 (16)	30 (46.9)	**4 vs 5 < 0.001**
LLD	10.1 ± 8.6	9.4 ± 8.5	12.9 ± 8.6	**.002***
LLV	406 ± 1123	287 ± 601	884 ± 2160	**<.001**#
TLV	429 ± 1128	311 ± 614	903 ± 2160	**<.001**#
LD	11.2 ± 34	7.9 ± 16.8	24.9 ± 67.1	**<.001**#
SVI, *n* (%)	40 (10.9)	25 (8.5)	15 (20.5)	**.003****
EPE, *n* (%)	81 (22)	57(19.3)	24 (32.9)	**.012****
LN, *n* (%)	48 (13)	37 (12.5)	11 (15.1)	.566**
Upgrade, *n* (%)	182 (49.5)	149 (50.5)	33 (45.2)	.417**
Specimen, *n* (%)				**<.001**a,b
GS				
3 + 3	66 (18)	65 (22)	1 (1.4)	
3 + 4	166 (45.1)	146 (49.5)	20 (27.4)	
4 + 3	95 (25.8)	64 (21.7)	31 (42.5)	
4 + 4	16 (4.3)	12 (4.1)	4 (5.5)	
4 + 5	25 (6.8)	8 (2.7)	17 (23.3)	
LVI	22 (6)	7 (2.4)	15 (20.5)	**<.001**b
PNI	337 (91.6)	265 (89.8)	72 (98.6)	**.015**#
Tm percent (%)	23 ± 19.1	19.4 ± 15.7	37.5 ± 24.2	**<.001**#
PSM	77 (20.9)	3/71 (4.1)	46 (63)	**<.001**#
EPE	134 (36.4)	81 (27.5)	53 (72.6)	**<.001**#
SVI	44 (12)	18 (6.1)	26 (36.1)	**<.001**#
T stage				**<.001**
2	211	200 (67.8)	11 (15.1)	**2 vs 3 < 0.001**
3	136	84 (28.5)	52 (71.2)	**2 vs 4 < 0.001**
4	21	11 (3.7)	10 (13.7)	
LN		3/71 (4.1)	5/30 (16.7)	**.043**b

No. patients (mean ± *SD*)	Total (*n*), 368	Non-BCR (*n*; %), 295 (80.1)	BCR (*n*; %), 73 (19.8)	*p*
Follow up time (month)	35.2 ± 16.7	35.8 ± 15.2	32.9 ± 21.5	.191[#]
Time to BCR (month)	11.5 ± 11.3	11.5 ± 11.3		

Note: Bold values indicate to emphasize the significance difference between two groups.

Abbreviations: BCR, Biochemical recurrence; BMI, body mass index; EPE, extraprostatic extention; GS, Gleason Score; LD, lesion density; LLD, largest lesion diameter; LLV, largest lesion volume; LN, lymph node invasion; LVI, lymphovascular invasion; mpMRI, multiparametric magneti resonance; NLR, neutrophil to lymphocyte ratio; PNI, perineural invasion; PSA, prostate spesific antigen; PSAd, PSA density; PSM, positive surgical margin; PV, prostate volume; SVI, seminal vesicle invasion; TLV, total lesion volume.

*Independent sample *t* test.

**Pearson χ^2.

[#]Mann Whitney *U* test.

[a]Except 2 vs. 4 and 3 vs. 4, all posthoc comparisons $p < .05$.

[b]Fisher exact test.

(Figure 2). All ML models outperformed the conventional statistical regression model in the prediction of BCR after prostatectomy.

4 | DISCUSSION

AI is a term used for computer technologies mimicking human cognitive functions such as making cause and effect relations and problem-solving.[18] This dynamic learning technology, which has to be evolved for accommodating ever-growing medical data, has started to reform our health systems, and it is a harbinger of new developments in this field.[19] The ML is a branch of AI. It can define the complex relationships between data and thus surpass the classical methods in constructing predictive models from a given data set.[19]

It was reported that the mean period between RP and BCR and distant metastasis was 8 years, while the mean period between metastatic disease and mortality was 5 years.[20] Prediction of BCR, which is one of the most significant markers of progression to mortality, has always been one of the goals of clinicians investigating PCa.[20,21] The predictive algorithms have the potential to determine the patients necessitating close follow-up and early intervention as needed.[22] Recently, relatively concise models such as the CAPRA scoring system have been developed instead of old methods, including Kattan nomograms and Han tables.[9,21,23,24] The new models were tried to be strengthened by integrating mpMRI findings and molecular assessment results to their format.[11,25]

The ML methods were previously used in urology practice to predict the urinary tract stone surgery outcomes, identify renal cell carcinoma subtypes and Fuhrman grade in renal cell carcinoma cases and anticipate complications in bladder cancer cases.[26] These methods were also used in the management of PCa patients.[26] This practice included detection of cancer in patients who underwent biopsy, prediction of PCa and its stage by mpMRI findings, and prediction of efficiency of radiotherapy. Hung et al.[27] investigated RARP parameters' relationship with postoperative outcomes by software integrated into robot systems and ML methods in a small patient series. They could predict the duration of hospital stay in 87.2% of cases by this model. Also, these authors were able to predict the postoperative urinary continence state by using early postoperative performance parameters in more than 85% of cases by employing the same model.[28] Wong et al.[2] worked on three different ML methods for predicting BCR within the first postoperative year by using 19 parameters in patients who underwent RP. In this study which included 338 patients, the ML methods K nearest neighbour (AUC = 0.903), Random Forest Classifier (AUC = 0.924), and logistic regression (AUC = 0.940) were able to predict BCR with a higher certainty than the other classical methods such as Cox Regression Analysis (AUC = 0.865). In our study, we included patients from all risk groups except for those with distant metastasis. We analyzed these patients using preoperative hematological parameters, mpMRI findings, and postoperative histopathological data with relatively long follow-up periods by similar ML methods. We also obtained more favorable results with the ML methods K nearest neighbour (AUC = 0.93), Random Forest Classifier (AUC = 0.95), and logistic regression (AUC = 0.93) than the classical Cox regression analysis (AUC = 0.91).

Our study's main strengths are the use of extensive patient data, a broad spectrum of inclusion and exclusion criteria, and a follow-up period of sufficient length for diagnosing or eliminating BCR. On the other hand, the primary limitation of our study is its retrospective design. It should also be considered that studies including more extensive PCa patient series with more extended follow-up periods will give more reliable information regarding the use of our model in clinical settings. Due to the development of these relatively new technologies and their integration into hospital information management systems, more accurate algorithms related to the diagnosis, treatment, and prognosis of the disease will be obtained. By connecting these methods with a common network on a national and even universal scale in the future, almost definite estimates will be made available to clinicians instantly. Considering that our

TABLE 2 Univariate and multivariate analysis to determine the predictors of biochemical recurrence

	Univariate			Multivariate		
	HR	95% CI	*p* value	HR	95% CI	*p* value
NLR	1.372	1.102–1.708	**.005**	1.474	1.007–2.157	**.046**
PSA	1.058	1.028–1.088	**<.001**			
PSAd	4.649	1.838–11.760	**.001**	0.000	0.000–0.309	**.027**
Gleason Score on biopsy	2.296	1.048–5.031	**.038**			
Tumour percent on biopsy	5.595	1.800–17.391	**.003**			
Risk	9.993	3.968–25.163	**<.001**	6.200	1.692–22.712	**.006**
mpMRI						
PIRADS	4.639	2.521–8.534	**<.001**	3.637	1.057–12.513	**.041**
LLD	1.043	1.011–1.076	**.008**			
LLV	1.000	1.000–1.001	**.006**			
TLV	1.000	1.000–1.001	**.006**			
LD	1.018	1.005–1.030	**.006**			
SVI	2.793	1.387–5.625	**.004**			
EPE	2.045	1.160–3.607	**.013**			
Specimen						
Gleason Score	3.158	1.577–6.332	**.001**			
LVI	10.640	4.155–27.251	**<.001**			
PNI	8.151	1.093–60.792	**.041**			
Tm percent	1.044	1.031–1.058	**<.001**			
PSM	14.509	7.935–26.531	**<.001**	27.651	9.609–79.570	**<.001**
EPE	7.001	3.942–12.435	**<.001**			
SVI	8.667	4.403–17.509	**<.001**	3.704	1.213–11.313	**.022**
LN	4.733	1.054–21.260	**.043**			
T stage	5.492	3.404–8.860	**<.001**	5.023	1.361–18.529	**.015**

Note: Bold values indicate to emphasize the significance difference between two groups.

Abbreviations: CI, confidence interval; EPE, extraprostatic extention; HR, hazards ratio; LD, lesion density; LLD, largest lesion diameter; LLV, largest lesion volume; LN, lymph node invasion; LVI, lymphovascular invasion; mpMRI, multiparametric magnetic resonance; NLR, neutrophil to lymphocyte ratio; PNI, perineural invasion; PSA, prostate spesific antigen; PSAd, PSA density; PSM, positive surgical margin; SVI, seminal vesicle invasion; TLV, total lesion volume.

TABLE 3 Classic Cox regression and machine learning algorithms for the prediction of biochemical recurrence

Algorithm	Accuracy	Sensitivity	Specifity	AUC
Classic Cox regression model	0.81	0.90	0.79	**0.91**
Random forest	0.86	0.88	0.85	**0.95**
Logistic regression	0.83	0.88	0.82	**0.93**
K-nearest neighbour	0.86	0.88	0.85	**0.93**

Note: Bold values indicate to emphasize the significance difference between two groups.

knowledge about optimal follow-up schemes of urogenital malignancies is limited, we believe that this technology will provide more useful information in the future.

5 | CONCLUSION

Despite the weaknesses mentioned above, we suggest that the construction of more reliable and potent models will provide the clinicians and patients with advantages such as more accurate risk classification, prognosis estimation, early intervention, avoidance of

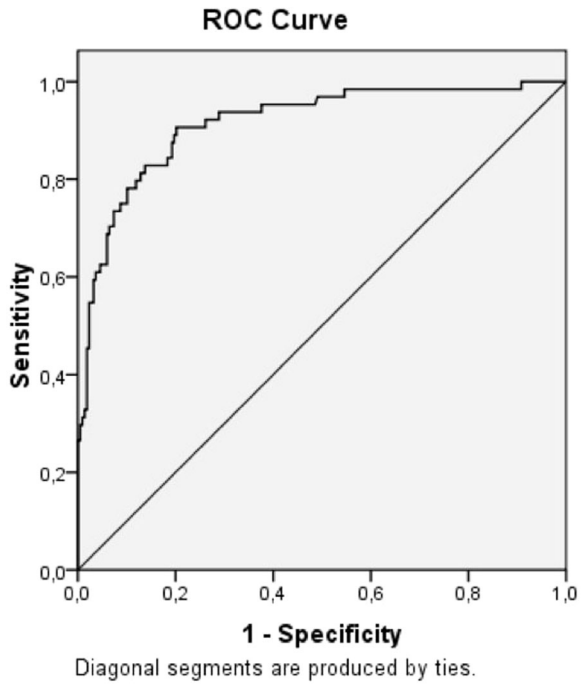

FIGURE 1 The area under the curve with Cox regression analyze

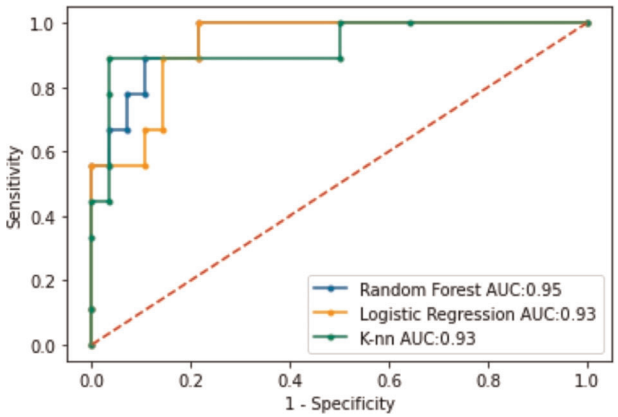

FIGURE 2 The area under the curve with machine learning algorithms [Color figure can be viewed at wileyonlinelibrary.com]

unnecessary treatments, relatively lower morbidity and mortality. The ML methods are cheap, and their powers increase with increasing data input; we believe that their clinical use will increase over time.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

Ethics committee approval was received for this study from the ethics committee of Health Science University, Bakırköy Dr. Sadi Konuk Training and Research Hospital. Written informed consent was obtained from patients who participated in this study.

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