EVALUATION OF PROSTAE SPECIFIC ANTIGEN (PSA) KINETICS IN PREDICTION OF PROSTATE CANCER PROGRESSION

by

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Abstract

Purpose

Serum prostate specific antigen (PSA) showed unfavorable accuracy to predict prostate cancer progression. With development of multidisciplinary medical science and impending need, the rate of serum PSA change "PSA kinetics" might be a potential biomarker to help predict. In this study we aim to evaluate the prediction accuracy of prostate-specific antigen velocity (PSAV) and prostate-specific antigen doubling time (PSADT) for low-risk prostate cancer progression among men in Active Surveillance Program from Johns Hopkins Hospital.

Methods

We evaluated 614 patients in the active surveillance program of Johns Hopkins Hospital from 1994 to 2012 who met the criteria of either low risk or very low risk prostate cancer. During the follow-up, prostate specific antigen (PSA) testing was performed twice every year, and 12-14 core biopsy was performed annually. The demographic and clinic relevant data were analyzed by univariate comparison methods and we used multivariate Cox proportional hazards analysis to calculate the association between PSA kinetics and disease progression and hazard ratio (HR) was the measure of association. Bootstrapping bias-corrected concordance index (c-index) was utilized to measure the ability of discrimination for prediction models. Subgroup analysis was done based on the serum PSA level at diagnosis, and sensitivity analysis was performed when biological relevant endpoints changed.

Results

In our dataset there were 208 (33%) participants among the 614 developing the progression either in terms of Gleason Score or prostate volume, the median follow-up time of the 614 participants was 2.4 years. Totally 7 prediction models were selected. For all-sample analysis PSAV calculated by averaging arithmetic method showed significance in multivariate prediction model (HR=1.43 ***P***=0.02 95%CI: 1.07, 1.92) if overall progression was treated as the endpoint. For subgroup with diagnostic PSA<4 ng/ml, 3 models were selected; and for subgroup with diagnostic PSA≥4 ng/ml, 2 models were selected. All these selected models had bias-corrected c-index over 0.70.

Conclusion

PSA kinetics can only show fair discrimination ability in aspect of low-risk prostate cancer progression regardless of biomedical endpoint or subgroup types used in the model. Pathological biopsy inspection should remain as the only reliable method to confirm disease progression.

Advisor/reader: Bruce J Trock, Hao Wang

Preface

Prostate cancer is one of the most prevalent cancer among the old men in United States. Over the past decades medical scientists and public health specialists spent so much time in improving the skills in treating this disease and trying to find out some other methods to prevent it. In terms of prevention, it was not only in primary prevention but also for secondary and clinical prevention which highly relied on biomarker and other non-invasive technique. And these days different places in the country use different kinds of methods to detect or predict the outcome of the disease. Some hospitals prefer using serum prostate specific antigen for screening while others would not; one eminent medical institution might support the use of PSA kinetics to predict disease outcome while the counterpart refused to do so. Choosing between different biomarkers in clinic is always the difficult thing, but it is these discrepancy and heterogeneity that made this topic amazing to scientific researchers, and I insisted on this topic until it become the core of my thesis. The main aim of this thesis is to analyze three different PSA kinetics in terms of their capability to predict low-risk prostate cancer progression. The dataset came from the Active Surveillance Program in Johns Hopkins Hospital and it took nine months to handle this data from logical checking, missing data handling to finalizing model. The statistical analysis is comprehensive and includes biomedical relevant variables. However there are still some limitations in this thesis and I would appreciate precious suggestion and comment when you finish the review.

Acknowledgement

I thank a lot for the faculty members from Johns Hopkins School of Public Health and School of Medicine who supported my research, particularly Dr. Bruce Trock and Dr. Hao Wang. I appreciate the help and support from my family and friends. Also I thank for the data from Johns Hopkins Hospital Active Surveillance Program.

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Background Introduction

Prostate cancer is the second leading cause of cancer death for men in United States. On average about one in six men will be diagnosed with this disease during their lifetime and 1 of 35 men will die[1]. Due to the severity and heavy burden of prostate cancer United State has approved that authorized hospital or health care center use serum PSA as a screening tool for prostate cancer since 1990's. However recently more and more studies have come up with the point that PSA screening can't reduce prostate cancer mortality and it will cause psychological and physiological harm. US Preventive Service Task Force (USPSTF) has done a meta-analysis based on 5 relevant trials and concluded that PSA screening is not effective in reducing prostate cancer mortality[2]. Also the serum PSA can increase as men get into the older age, particularly for those non-tumor patients with benign prostate hypertrophy and their serum PSA values will approximately increase at a speed of 0 .75 ng/ml/year[3,4]. This can greatly reduce its sensitivity and specificity in screening or disease status prediction[5]. So far with the development of quantitative skills and the existing impending need for reliable biomarker, the change of serum PSA level which could be referred to as PSA kinetics (PSAV and PSADT) were employed to predict the disease status and disease progression. As early in 2005 Dr Anthony D'Amico and colleagues claimed that the rate of serum PSA change could be a biomarker to help clinicians predict cancer mortality. They also found low-risk prostate cancer patients with PSAV over 2.0 ng/ml/yr can have a disease specific death rate of 19% at seven years whereas this rate was 0 in patients with PSAV lower than 2.0ng/ml/yr[6]. In 2006, Klotz et al. reported PSA kinetics and its role in active surveillance. They concluded that PSA kinetics could be a supportive tool in prediction of

disease recurrence or progression[7]. Furthermore several following studies also identified the value of PSA kinetics in the clinic. PSA kinetics may allow detection of disease progression or cancer stage change in active surveillance patients, which would allow intervention at an early stage so that undesirably high mortality rate can be prevented. But until now, as the same as serum PSA, PSA kinetics received more controversy than its praise. Several epidemiological and clinical researches have investigated PSAV and PSADT's ability in disease progression prediction, but most of them disputed the reliability of PSA kinetics for prognosis. There were 3 cohort studies that analyzed the association between PSA kinetics and prostate cancer progression but none of them gave strong evidence to show a reliable prediction power in PSA kinetics[8,9,10]. Vickers and his colleagues provided evidence through general and systematic review to declare that PSA kinetics can predict very few in aspect of prognosis for pre-treatment patients beyond serum PSA alone[11,12]. However although there were a great many sources doubting about PSA kinetics prediction power, there is rationale that could be argued about. First for all the three cohort study mentioned above, all of them had very small sample size and the biggest one was just 408 and this increased imprecision. Secondly, two of them (Ross 2010, Iremashvili 2012) didn't use statistical model to provide adjusted measure of associations that made the result less convincible. One (Whitson 2011) used logistic regression method which was not the best choice for time-to-event data, therefore it was not the risk but rate of the event that disclosed better epidemiology significance. The systematic review (Roger Chou 2011) seemed to be plausible but the internal heterogeneity between each individual study made it hard to pool the outcome thus it only provide qualitative synthesis. One thing more, none of these studies have done

validation to check prediction accuracy. Therefore there is still some necessity to do our research based on the Johns Hopkins Active Surveillance Program for prostate cancer to analyze how good PSA kinetics can predict malignant outcomes in prostate cancer patients.

Objective

In this study our primary aim is to investigate if different types of PSA kinetics could give us a good prediction of progression among men with low or very low risk prostate cancer within Johns Hopkins Active Surveillance Program.

Methods

Participants in Active Surveillance

The Active Surveillance Program of Johns Hopkins Hospital started from early 1990's and men who meet the criteria of low risk prostate cancer in the program (life expectancy less than 10-15 years; stage T1c or T2a; PSA≤10ng/ml; Gleason score (GS) ≤6 with no Gleason pattern 4 or 5 on at least a 12 core biopsy or very low risk prostate cancer could be enrolled) or very low risk prostate cancer in the program (life expectancy less than 20 years; stage T1c; PSA density <0.15 ng/ml/cm^3; Gleason score ≤6 with no Gleason pattern 4 or 5; ≤2 cores with cancer, or cancer involving ≤50% of any core on at least a 12 core biopsy) were enrolled for follow-up[13,14], and these criteria can be found on Johns

Hopkins Hospital official website. The men who were in the Active Surveillance Program would take serum PSA measurement and digital rectal exam (DRE) every 6 months and every year participants took 12-core biopsy from the tumor tissue. Curative intervention would be suggested if unfavorable biopsy results were confirmed (including Gleason score > 6, or involvement of tumor > 2 cores, or percentage of involvement > 50% in any of the core). The Gleason Score was utilized as the primary tool to evaluate prostate cancer progression and this determination was based on the microscopic pathologic feature of tissues taken from biopsy. The scale of Gleason grade ranges from 1-5. A five in the Gleason grade indicates the lack of normal glands cells. In the 12 biopsy cores from prostate, the most prevalent Gleason grade pattern of cells type and second most prevalent cell type will be added together to determine the combined GS. The combined score will range from 2-10, although in practice pathologists don't report Gleason scores lower than 6. For instance, a Gleason Score of 7 can be 4+3[15], and this score indicates that the grade 4 cell-pattern is the most prevalent one and grade 3 cell-pattern ranks second. From pathological perspective it could help for predicting the outcomes of patients. Progression by GS was defined as any core from biopsy has the Gleason Score over 6 and progression by tumor volume was defined as number of positive core from biopsy greater than 2 or maximum percentage core involvement with tumor greater than 50%, and the overall progression is term to define progression type that meets both or either of these definitions. The active surveillance program is an approved option for management of low or very low risk prostate cancer by Johns Hopkins Hospital, and all participants have signed an IRB-approved consent form allowing their information to be used in research.

Data Collection

Demographic data like age and race were collected directly from electronic medical record. The post-diagnosis serum PSA level, PSA density, maximum percentage of tumor involvement, number of positive core, Gleason Score from annual biopsy, and PSA kinetics value were recorded in the active surveillance cohort clinical database. The confirmation of disease progression was determined by clinical pathologists based on either unfavorable Gleason Score or biopsy tumor volume, as described above.

Statistical Analysis

STATA 12.0 was used to perform statistical analysis. We analyzed 614 pre-treatment patients who have participated in Active Surveillance Program in Johns Hopkins Hospital between 1994 and 2012, and missing data for each case was carefully considered and handled through conditional mean imputation based on non-missing covariates. In univariate statistic analysis, Kurtosis and Skewness test were firstly performed to identify the distribution normality of continuous variables including age at diagnosis, post-diagnosis PSA level, PSA density (PSAD) at diagnosis, PSAV calculated by regression, PSAV calculated by arithmetic method, PSADT, number of positive core at biopsy and maximum percentage of involvement of tumor tissue from biopsy. Non-parametric Wilcoxon rank sum test was done to judge if there was significant difference in continuous variables between people with disease progression and those without. Chi-square test was utilized to verify the substantial association between disease progression and categorical variables, and there were two categorical variables “whether the patient is white” and “whether the tumor is very low risk prostate cancer”. All these univariate tests

were two-sided, and P value less than 0.05 was considered as threshold of statistical significance for all tests. Kaplan-Meier survival analysis was done to get an overview of the time-to-event information of the disease in all patients and subgroup patients. We have three different biomedical endpoints in our dataset: overall progression, progression by GS and progression by tumor volume (TV). These biomedical endpoints were used in Cox proportional hazard analysis in multivariate and sensitivity analysis. For the calculation of PSAV, only serum PSA measurements acquired at or after diagnosis were utilized. PSAV was calculated in two ways: The PSAV by averaging method (PSAV-AVE) was calculated by average of the rate of change over at least three consecutive measurement of serum PSA, using arithmetic equation of change in PSA over time [1/(n-1)]*(sum of slopes in function of PSA vs measurements between two consecutive PSA measurement) and PSA by regression slope (PSAV-SLOPE) was calculated by using serum PSA multiplied by the slope of a linear regression of ln(PSA) during follow-up[8,14]. PSADT was calculated by ln(2) divided by the slope of regression of ln(PSA) on serum PSA measurement over time in the surveillance procedure[8,16]. Univariate Cox proportional hazard analysis was used to analyze the association between PSA kinetics and disease progression, and it was measured as hazard ratio (HR). Confounding factors were confirmed according to three issues: show a significant association with the progression in univariate analysis; the HR of PSA kinetics in univariate Cox proportional hazard analysis changed over 10% after adding the potential confounding covariate; biomedical reasonability. Confounding variables were added into multivariate Cox proportional hazard analysis model to be adjusted. To assess the model accuracy and prediction accuracy of Cox proportional hazard model including PSA kinetics,

concordance index (c-index) was used as a measurement to quantify the accuracy in aspect of discrimination which has a similar interpretation of area under receiver operating curve (ROC)[17]. The c-index ranges from 0.5-1.0, a value of 0.5 will have the indication of no predictive discrimination for the model; also the accuracy will be considered poor if it is smaller than 0.6 and a value of 1.0 means perfect ability for the model to rank people with different outcome. 500 times bootstrapping was utilized to calculate the bias-corrected concordance index for internal validation. Subgroup analysis was performed in men with initial diagnostic serum PSA ≥ 4ng/ml and men with initial serum PSA < 4ng/ml because according to prior research9 PSA kinetics, particularly PSAV, will depend on the value of initial serum PSA level. To enhance clinical significance we compared analytical results when treating PSA kinetics as continuous variable with results when treating them as categorical variables. PSA kinetics were transformed into categorical variables based on certain cut-offs. For PSADT we used 4 year as the cut-off regardless of initial diagnostic PSA level. For all patients and the subgroup with diagnostic PSA level≥4 ng/ml, the cutoff of PSAV would be 0.75 ng/ml/year, and if initial PSA level<4 ng/ml then we use 0.4ng/ml/year as the cutoff. All the choice above were based on previously published research[8,18,19,20]. In subgroup analyses based on initial diagnostic PSA, the same set of statistical procedures were performed including Cox proportional hazard analysis and cross-validation. Sensitivity analysis was done based on alternate biomedical endpoints. Specifically we treat overall progression, progression by Gleason score and progression by tumor volume as the endpoint in Cox proportional hazard analysis model respectively. What is more since Vickers et al[12] claimed that serum PSA alone could provide sufficient information about

prostate cancer without the help of kinetics, we tried to test the model's prediction accuracy by comparing the c-index for models with PSA and PSA kinetics to models with PSA alone in the Cox proportional hazard analysis model.

Model Selection

The principle of selection was determined by the discrimination ability and the simplicity rationale. Prediction model was selected based on bias-corrected c-index after bootstrapping and the number of covariate in the model, and c-index<0.70 will be considered as an indicator of poor ability for discrimination.

Results

Of the total 614 men in the cohort, 208 (33%) of them had disease progression in either form. Among them, 36 progressed by Gleason score (GS), 133 progressed by tumor volume (TV), 39 progressed by both definition. In the overall study population, the mean and standard deviation (SD) of age at diagnosis was 64.85 years and 5.76 years, and the mean and SD of serum PSA at diagnosis was 5.02 ng/ml and 2.87 ng/ml. The median follow up time was 2.42 years, ranging from 0.27 to 12.99 years. Kaplan-Meier curve was utilized to depict the overall progression condition along with the follow-up year, and the curves were similar between the condition where overall progression was the endpoint and where progression by tumor volume was the endpoint in respect of median progression time (figure 1 and 3). The Kaplan-Meier curve had another shape when we treated progression by GS as the endpoint (figure 2). When we used overall progression

or progression by tumor volume as the endpoint, the Kaplan-Meier curve went down more quickly compared to Kaplan-Meier curve when we use progression by Gleason score as the endpoint. Also the median progression time for progression by Gleason score was longer than the other two types of progression, for progression by Gleason score the median time was approximately 11 years while it was about 6 years for overall progression and 8 years for progression by tumor volume.

The table1-table3 compared the basic demographic and clinical characteristics between all the patients with and without overall disease progression. For them, there were significant differences between people who have overall progression and those not in aspects of PSA kinetics (PSADT $\boldsymbol{P}<0.001$, PSAV-SLOPE $\boldsymbol{P}<0.001$, PSAV-AVE $\boldsymbol{P}=0.02$) but the diagnostic PSA was not significantly associated with overall progression status ($\boldsymbol{P}=0.252$). When changing the comparison criteria by alternate endpoints to progression by GS, the association between PSA at diagnosis and PSA kinetics turned to non-significant (table 2). And when we chose progression by tumor volume as the endpoint, the association between progression status and PSA at diagnosis and PSA kinetics become significant (table 3). Because the distribution of PSA and related kinetics followed non-normalized distribution thus standard error was not so significant, in this case the distribution of the variables become more important and it could be better observed in boxplot as an ancillary descriptive tool (figure 4-6).

According to the result from univariate analysis and the change of kinetics' HRs in univariate Cox proportional hazard analysis, we confirmed the essential covariates to be controlled in multivariate model. For all the 614 patients if we treat overall progression and progression by tumor volume as the endpoints then same set of covariate would be controlled (PSA at diagnosis, number of positive core and maximum percentage of tumor involvement) (table 10 and 12), but we only controlled for PSA at diagnosis if progression by GS was then endpoint (table 11). Concordance index and bias corrected c-index were available in the tables. In models where we treated overall and tumor volume progression as the endpoint, bias-corrected c-indexes were all beyond 0.70, but when endpoint changed to progression by GS bias the highest c-index was only 0.601 indicating a poor separation ability. As a whole, when deleting PSA kinetics from original multivariate model the c-index would decrease so we included PSA kinetics in these models. Model A and B were selected based on our principle, and they both have fair discrimination ability (c-index was 0.702 and 0.732 respectively). No model was selected to predict progression by GS due to the poor discrimination ability in all three kinetics in this scenario (table 10). The HR for overall progression when PSAV-AVE greater than 0.75 ng/ml/yr after adjusting for other confounders was 1.43 (***P***=0.02 95%CI: 1.07, 1.92) and HR for progression by tumor volume by this cutoff was 1.54 (***P***=0.25 95%CI: 1.12, 2.11) in the models (Part A in table 10).

Subgroup Analysis

In subgroup analysis there were 208 with diagnostic serum PSA< 4 ng/ml, and there were 54 (25.96%) of them had disease progression (38 progressed by tumor volume, 9

progressed by GS and 7 progressed by both definitions). As a whole the diagnostic PSA and PSA kinetics were not as tightly associated with progression status as the whole sample. The diagnostic serum PSA level only showed significant association with the overall progression status (***P***=0.037) and progression by tumor volume (***P***=0..021) (table 4 and 6), however there was no significant association between PSA kinetics and any kind of disease progression status in this subgroup of people (table 4-6) and the difference in distribution of PSA and relevant kinetics could be observed in boxplots (figure 7-9). According to bias-corrected c-index and simplicity we chose model C, D and E for this subgroup to predict overall progression, progression by GS and progression by tumor volume (table 11), and their c-indexes were 0.721, 0.739 and 0.742 indicating acceptable separation capability. But although these models showed fair discrimination ability, none of them provided evidence to support kinetics significance in prediction. When using overall progression as the endpoint for this subgroup, the HR for progression when PSADT is larger than 4 years is 1.05 (***P***=0.34 95%CI: 0.55, 1.98) showing non-significant association; for progression by GS, PSAV-SLOPE cutoff was used as the predictor in the set which has a HR of 2.45 (***P***=1.32 95%CI: 0.85, 7.04); and for progression by tumor volume, PSADT had HR of 1.25 (***P***=0.48 95%CI: 0.59, 2.65) (Part B of table 11).

There were 408 males with diagnostic serum PSA ≥4ng/ml, and 154 of them had progression (37.74%). Among these progressed individuals 27 had progression by GS, 95 had progression by tumor volume and 32 had progression by both definitions. In

univariate analysis the outcome was similar to that of all sample analysis. All PSA kinetics showed significant association (P value < 0.05) between disease status when we treated endpoint as overall progression or progression by tumor volume. There was no significant association between PSA kinetics and progression by GS in this subgroup of patients (table 7-9). Boxplots of diagnostic PSA and PSA kinetics could show the distribution in a direct way in figure 10-12. The model selection process was similar to that of all-sample analysis, and in each set of endpoint type model we controlled for exactly the same set of covariate. No prediction model was selected to predict for progression by GS in this subgroup of people due to the worthless discrimination ability reflected by their low bias-corrected c-index (table 12). In model F (Part B of table 12) when we use 0.75 ng/ml/yr as cutoff of PSAV, the HR for overall progression by PSAV-AVE was 1.38 (***P***=0.06 95%CI: 0.99, 1.94); and in model G (Part B of table 12) the HR for progression by tumor volume when PSAV-AVE above the cutoff was 1.55 (***P***=0.02 95%CI: 1.08, 2.24). Both these two models had acceptable c-index for discrimination, the index for model F was 0.716 and model G was 0.751.

Sensitivity Analysis

Due to previous clinic and epidemiology research[12], there is evidence that PSA kinetics were tightly connected with the initial diagnostic serum PSA value which could possibility predict biomedical relevant event alone. In all-sample and subgroup analysis we tried to delete PSA kinetics from original model to see if the model's prediction accuracy will change. And according to the statistical result (table 10-12), for most circumstances c-indexes (bias-corrected) were decreased to a slight or moderate degree

when we removing PSA kinetics from original models. And this phenomenon, to some extent, supported the necessity to combine serum PSA with PSA kinetics when building the model.

Discussion

In United States PSA kinetics, as well as other PSA related biomarkers, were used in clinic and community-based study to predict and monitor prostate disease status providing evidence for clinic practice and health intervention. However, even until now there is too much heterogeneity in opinions regarding the appropriateness of PSA kinetics usage, and there is big discrepancy between different institutions. Using the dataset from Active Surveillance Program in Johns Hopkins Hospital, only three out of seven finalized prediction models showed clear statistical significance of PSA kinetics in progression prediction ($P<0.05$) and one showed marginal significance ($0.05<P<0.10$). But even though not all models showed significance in terms of PSA kinetics, they all provided at least an acceptable capability to make separation between patients who had the progression and those who didn't and all these seven models had bias-corrected c-index over 0.70. One feature of these models was that most of them were controlled for other covariate particularly the number of positive core and maximum percentage of core involvement from biopsy, and that may be because these two parameters are indicators of tumor growth thus connected with tumor's bio-physiological behavior. In general, based on methodological perspective model A (model of effect of PSADT on overall progression for all patients) would be the best choice to predict overall progression

among all-sample patients for it has a c-index over 0.70 which is an indicator of worthiness, also the PSAV-AVE showed significant statistical association in predicting the result. Furthermore it has the least number of parameters in the model that is less redundant than the others. Model G (model of effect of PSAV-AVE on progression by tumor volume for subgroup of patients with diagnostics PSA≥4 ng/ml) would be the proper choice to predict progression by tumor volume among patients with diagnostic PSA<4 ng/ml for its high c-index (>0.750) and significant HR for PSA kinetics. Although other models also have c-index over 0.70, some of them are too redundant in aspect of numbers of parameters or the PSA kinetics in these models showed no significant association measure. Additionally only model D (model of effect of PSAV-SLOPE on progression by GS for subgroup of patients with diagnostics PSA<4 ng/ml) was aimed to predict progression by Gleason score, however due to the pathological related biopsy limitation and non-significant association measure within the model, it would not be reliable from statistical perspective thus would not be suggested to be utilized to predict the disease progression status.

In our study, we identified three endpoints during analysis, it was very necessary because they all have essential underlying clinical significance, they could also offer physicians and epidemiologists with indispensable disease information. For patients with progression by GS, in their biopsy result they should have at least one core having the tumor with GS over 6. And this progression type could give us information about how malignant the tumor will be including cellular biological behavior and histological traits,

which can help oncologists to determine the proper treatment regimen. However the biopsy can sometimes underestimate the tumor grade providing us with a favorable perspective about disease which is actually not true. This phenomenon can happen because prostate is an organ located in our pelvic region which can only be touched through transrectal ultrasound (TRUS) guided biopsy. But from the anatomy perspective due to its multifocal structure and the uncertainty about complete sampling during biopsy, the most biologically important pattern may be located in the inner area of prostate tissue that was not taken by the pathologists[21,22]. In 1992 Gleason has reported that patients biopsy results were not always in good concordance with the prostatectomy result[23]. Gofrit et al[24] reported from the prospective cohort study consisting of 448 people illustrated that there was over 20% risk that patients with a biopsy Gleason Score over 6 were actually concealing more serious pattern and would upgrade in future. In 2012 Mehta[25] reported similar result that 32.7% of their research cohort men experience an upgrade from GS6 to higher grade. Additionally, King found in his research that the outcome of sextant biopsy scheme which was a popular choice among urologists had an undesirable correlation with the outcome from prostatectomy in aspect of Gleason Score (28%-45%)[26]. And Mian found that even we use extended biopsy scheme the correlation still could hardly get beyond 70%[27]. Therefore this can lead to unfavorable misclassification between low-risk cancer patients and those with more aggressive disease. Aggressive disease patients with higher PSAV or PSADT might be classified as low-risk patients at the early visits who actually owned the GS at or over 7, and even in later period when they could be examined to have GS at or over 7 the “non-progression” time increased. When these were considered the effect size of PSA kinetics in model

predicting progression by GS could be underestimated, and it could delay prompt treatment in clinic which is another essential topic in urology.

Our study has several strengths. First we had a relatively larger sample size over 600 participants which could reduce the imprecision and make our conclusion more reliable. Secondly unlike previous studies in similar topic, we used three types of progression in the Cox model to help understand pathogenesis mechanism as well as its epidemiological significance. Iremashvili et al had done a research of same topic in 2012 finding that PSA kinetics unreliable biomarker in separating between progressed and non-progressed individuals[8]. However in this study only the definition of overall progression was utilized combing progression by GS which could finally compromise the discrimination through inevitable misclassification. Additionally patients with maximum core involvement over 20% were defined as progressed ones which was not unusual for some low-risk prostate cancer patients in Johns Hopkins Hospital, so there could be an improvement of this study in aspect of PSA kinetics prediction accuracy when these were considered. Third, in our study we compared the PSAV calculated by two methods and found that PSAV by averaging arithmetic method performed better in discrimination, and this result is different from previous research. Benecchi et al has conducted a research based on 312 male to compare the separation power of PSAV calculated by regression slope and arithmetic equation[28] in aspect of prostate cancer diagnosis. It was found in Benecchi's study that PSAV calculated through regression slope had a better separation ability than PSAV calculated by arithmetic equation both in sensitivity and specificity, the ROC area

for PSAV-SLOPE was 0.743 and PSAV-AVE was 0.663. In 2006, Connolly16 had done a similar study with a sample of 2204 to discuss about discrepancy between PSAV calculation methods in aspect of prostate cancer diagnosis, and he found that PSAV-SLOPE showed a better discrimination ability than PSAV-AVE. However in their studies the aim was to make diagnosis rather than predict prognosis, thus for their participants there would be more proportion of serum PSA that were generated by the normal tissue than the malignant tissues. In fact, according to O'Brien and his colleagues research[29] there were 8 ways to define PSAV, but over half of them are not suitable for active surveillance because of the restriction of PSA testing before cancer diagnosis. Some calculation methods required certain interval that don't fit Johns Hopkins Hospitals scenario. Also according to some research evidence[16,30], prostate cancer patients serum PSA can increase at a very fast speed sometime during the pathogenesis that the function of serum PSA on time converted to exponential indicating there are some underlying substantial difference in aspect of PSA in people with pre-malignant disease and people who already had the cancer, and we think that would be a rationale to explain the difference in aspect of PSAV between previous studies. Furthermore, our study employed bootstrapping method to calculated bias-corrected c-index so that it could do cross-validation and tell us how reliable our prediction model will be.

However there were still some limitations of our study. First when treating PSA kinetics as categorical variables, we used certain cutoff based on previous literature[19,20]. However the cutoff in these studies were aimed to help make diagnosis among a group of normal

people. Based on biochemical perspective the tumor cell expressed more PSA than normal tissue cells, so the speed for PSA increase will be different from those normal people. Therefore our cutoffs for prognosis should have been elevated a little based on the ones used in screening or diagnostic studies. Secondly, in our study conditional mean imputation was utilized to handle the missing value particularly PSA kinetics. Unlike multiple imputation, the conditional mean imputation replace the missing items according to regression fitted value. In this scenario imputed value can not have the error term, therefore these estimations are going to be perfectly along with regressive function line without residual variance. This will give rise to greater precision in these data which would be considered as over-precise without uncertainty. As the consequence the 95% confidence interval in the outcome were narrower, so for model A, B and G the significance of PSAV-AVE should be examined in future researches. At last, there was an unavoidable selection bias that over 90% of people in our study are white people which decrease the representativeness of our study. Because the enrolled white patients might have different social economic status than other race who were not enrolled, thus there could be a bias that should be carefully handle in future study.

Conclusion

PSAV and PSADT were both not reliable enough to predict low-risk prostate cancer progression in Active Surveillance, and they can only provide a fair power for discrimination. TRUS directed prostate biopsy is indispensable when determining the disease status. Further study should be done to analyze the proper kinetics cutoff for

clinic usage when judging disease progression and also analyze how they performed among patients with different races.

Table 1 Univariate analysis compare variables between 614 active surveillance patients with and without overall progression

Characteristics	No Progression		Progression		P Value
	406		208		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	64.43	5.70	65.68	5.80	0.019
PSAD at diagnosis, ng/ml/cm^3	0.10	0.06	0.12	0.06	0.002
PSA at diagnosis, ng/ml	4.96	3.02	5.14	2.57	0.252
Percentage of involved core	6.27	9.04	14.59	19.56	<0.001
Number of positive core	1.12	0.33	1.59	0.99	<0.001
PSADT, years	11.32	18.70	10.23	17.75	<0.001
PSAV_slope, ng/ml/yr	-0.02	1.94	0.65	1.94	<0.001
PSAV_ave, ng/ml/yr	-0.63	8.22	-0.29	4.98	0.020
Categorical					
Race					
White	374(67.63%)		179(32.37%)		0.017
Non-white	32(52.46%)		29(47.54%)		
Cancer risk at enrollment					
Very low risk	322(70.93%)		132(29.07%)		<0.001
Low risk	84(52.50%)		76(47.50%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 2 Univariate analysis compare variables between 614 active surveillance patients with and without progression by GS

Characteristics	No Progression by GS		Progression by GS		P Value
	539		75		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	64.80	5.76	65.20	5.77	0.484
PSAD at diagnosis, ng/ml/cm^3	0.11	0.06	0.12	0.07	0.021
PSA at diagnosis, ng/ml	4.94	2.82	5.55	3.18	0.105
Percentage of involved core	9.10	14.65	9.00	9.24	0.042
Number of positive core	1.28	0.69	1.27	0.53	0.479
PSADT, years	11.35	19.51	8.09	4.55	0.166
PSAV_slope, ng/ml/yr	0.16	1.96	0.54	1.98	0.087
PSAV_ave, ng/ml/yr	-0.50	7.58	-0.57	4.64	0.617
Categorical					
Race					
White	490(88.61%)		63(11.39%)		0.061
Non-white	49(80.33%)		12(19.67%)		
Cancer risk at enrollment					
Very low risk	399(87.89%)		55(12.11%)		0.90
Low risk	140(87.5%)		20(12.5%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 3 Univariate analysis compare variables between 614 active surveillance patients with and without progression by tumor volume

Characteristics	No Progression by TV		Progression by TV		P Value
	442		172		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	64.41	5.74	65.99	5.68	0.005
PSAD at diagnosis, ng/ml/cm^3	0.11	0.06	0.11	0.06	0.008
PSA at diagnosis, ng/ml	5.00	3.03	5.06	2.42	0.448
Percentage of involved core	6.40	9.10	15.99	20.78	<0.001
Number of positive core	1.13	0.34	1.66	1.06	<0.001
PSADT, years	11.09	17.98	10.61	19.42	<0.001
PSAV_slope, ng/ml/yr	-0.0002	1.98	-0.73	1.82	<0.001
PSAV_ave, ng/ml/yr	-0.69	8.06	-0.06	4.74	0.014
Categorical					
Race					
White	404(73.06%)		149(26.94%)		0.076
Non-white	38(62.30%)		23(37.70%)		
Cancer risk at enrollment					
Very low risk	349(76.87%)		105(23.13%)		<0.001
Low risk	93(58.13%)		67(41.88%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 4 Univariate analysis compare variables between 208 active surveillance patients with and without overall progression among those with diagnostic PSA<4 ng/ml

Characteristics	No Progression		Progression		P Value
	154		54		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	63.48	5.77	65.34	5.94	0.057
PSAD at diagnosis, ng/ml/cm^3	0.07	0.05	0.08	0.04	0.141
PSA at diagnosis, ng/ml	2.27	1.06	2.64	0.88	0.037
Percentage of involved core	6.17	8.78	12.25	17.22	0.007
Number of positive core	1.12	0.33	1.65	1.08	<0.001
PSADT, years	10.80	15.27	12.45	27.38	0.053
PSAV_slope, ng/ml/yr	0.15	1.05	0.41	0.91	0.183
PSAV_ave, ng/ml/yr	0.35	2.50	0.23	1.34	0.681
Categorical					
Race					
White	141(75.4%)		46(24.6%)		0.181
Non-white	13(61.9%)		8(38.1%)		
Cancer risk at enrollment					
Very low risk	140(77.35%)		41(22.65%)		0.005
Low risk	14(51.85%)		13(48.15%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 5 Univariate analysis compare variables between 208 active surveillance patients with and without progression by GS among those with diagnostic PSA<4 ng/ml

Characteristics	No Progression by GS		Progression by GS		P Value
	192		16		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	63.87	5.79	65.16	6.75	0.442
PSAD at diagnosis, ng/ml/cm^3	0.07	0.05	0.07	0.03	0.813
PSA at diagnosis, ng/ml	2.36	1.03	2.46	1.04	0.751
Percentage of involved core	7.81	12.14	7.00	7.52	0.564
Number of positive core	1.26	0.67	1.31	0.48	0.237
PSADT, years	11.55	19.79	7.33	5.32	0.182
PSAV_slope, ng/ml/yr	0.18	1.01	0.61	1.09	0.272
PSAV_ave, ng/ml/yr	0.29	2.29	0.65	1.81	0.491
Categorical					
Race					
White	173(92.51%)		14(7.49%)		0.668
Non-white	19(90.48%)		2(9.52%)		
Cancer risk at enrollment					
Very low risk	165(91.16%)		16(8.84%)		0.235
Low risk	27(100%)		0(0%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 6 Univariate analysis compare variables between 208 active surveillance patients with and without progression by tumor volume among those with diagnostic PSA<4 ng/ml

Characteristics	No Progression by TV		Progression by TV		P Value
	163		45		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	63.60	5.87	65.31	5.69	0.089
PSAD at diagnosis, ng/ml/cm^3	0.07	0.04	0.08	0.04	0.071
PSA at diagnosis, ng/ml	2.27	1.05	2.70	0.82	0.021
Percentage of involved core	6.13	8.68	13.59	18.36	0.003
Number of positive core	1.13	0.34	1.73	1.16	<0.001
PSADT, years	10.56	14.90	13.65	29.86	0.135
PSAV_slope, ng/ml/yr	0.16	1.03	0.40	0.97	0.344
PSAV_ave, ng/ml/yr	0.36	2.44	0.18	1.39	0.442
Categorical					
Race					
White	148(79.14%)		39(20.86%)		0.061
Non-white	15(71.43%)		6(28.57%)		
Cancer risk at enrollment					
Very low risk	149(82.32%)		32(17.68%)		0.90
Low risk	14(51.85%)		13(48.15%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 7 Univariate analysis compare variables between 406 active surveillance patients with and without overall progression among those with diagnostic PSA≥4 ng/ml

Characteristics	No Progression		Progression		P Value
	252		154		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	65.00	5.59	65.80	5.76	0.258
PSAD at diagnosis, ng/ml/cm^3	0.12	0.06	0.13	0.06	0.247
PSA at diagnosis, ng/ml	6.60	2.62	6.01	2.39	0.003
Percentage of involved core	6.34	9.21	15.41	20.30	<0.001
Number of positive core	1.11	0.33	1.56	0.96	<0.001
PSADT, years	11.64	20.55	9.46	12.80	<0.001
PSAV_slope, ng/ml/yr	-0.12	2.32	0.73	2.18	<0.001
PSAV_ave, ng/ml/yr	-1.22	10.21	-0.47	5.73	0.003
Categorical					
Race					
White	233(63.66%)		133(36.34%)		0.045
Non-white	19(47.50%)		21(52.50%)		
Cancer risk at enrollment					
Very low risk	182(66.67%)		91(33.33%)		0.006
Low risk	70(52.63%)		63(47.37%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 8 Univariate analysis compare variables between 406 active surveillance patients with and without progression by GS among those with diagnostic PSA≥4 ng/ml

Characteristics	No Progression by GS		Progression by GS		P Value
	347		59		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	65.32	5.69	65.21	5.54	0.976
PSAD at diagnosis, ng/ml/cm^3	0.12	0.06	0.14	0.07	0.100
PSA at diagnosis, ng/ml	6.37	2.46	6.39	3.05	0.450
Percentage of involved core	9.82	15.84	9.54	9.64	0.070
Number of positive core	1.29	0.70	1.25	0.54	0.902
PSADT, years	11.24	19.38	8.29	4.35	0.177
PSAV_slope, ng/ml/yr	0.15	2.32	0.52	2.16	0.177
PSAV_ave, ng/ml/yr	-0.94	9.27	-0.90	5.10	0.658
Categorical					
Race					
White	317(86.61%)		49(13.39%)		0.048
Non-white	30(75.00%)		10(25.00%)		
Cancer risk at enrollment					
Very low risk	234(85.71%)		39(14.29%)		0.840
Low risk	113(84.96%)		20(15.04%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 9 Univariate analysis compare variables between 406 active surveillance patients with and without progression by tumor volume among those with diagnostic PSA≥4 ng/ml

Characteristics	No Progression by TV		Progression by TV		P Value
	279		127		
Continuous	Mean	SD	Mean	SD	
Age at diagnosis, years	64.88	5.62	66.23	5.67	0.057
PSAD at diagnosis, ng/ml/cm^3	0.13	0.06	0.13	0.06	0.521
PSA at diagnosis, ng/ml	6.60	2.65	5.89	2.25	0.002
Percentage of involved core	6.56	9.35	16.84	21.58	<0.001
Number of positive core	1.13	0.34	1.63	1.02	<0.001
PSADT, years	11.40	19.57	9.53	14.00	<0.001
PSAV_slope, ng/ml/yr	-0.10	2.36	0.85	2.03	<0.001
PSAV_ave, ng/ml/yr	-1.29	9.92	-0.15	5.46	0.001
Categorical					
Race					
White	256(69.95%)		110(30.05%)		0.061
Non-white	23(57.50%)		17(42.50%)		
Cancer risk at enrollment					
Very low risk	200(73.26%)		73(26.74%)		0.90
Low risk	79(59.40%)		54(40.60%)		

*Wilcoxon rank sum and Chi-square test were used for continuous and categorical variables respectively

Table 10

Part A All-sample analysis for 614 active surveillance patients

Endpoint	Target PSA Kinetics	Covariate including in the prediction model	C-index	C-index w/o kinetics
Overall Progression	PSADT≥4 year	PSA at diagnosis, MXPT, dxPOS	0.700	0.696
	PSAV_SLOPE ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.701	0.696
	PSAV_AVE[A] ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.702	0.696
Progression by GS	PSADT≥4 year	PSA at diagnosis	0.563	0.556
	PSAV_SLOPE ≥0.75 ng/ml/yr	PSA at diagnosis	0.601	0.556
	PSAV_AVE ≥0.75 ng/ml/yr	PSA at diagnosis	0.582	0.556
Progression by TV	PSADT≥4 year	PSA at diagnosis, MXPT, dxPOS	0.725	0.725
	PSAV_SLOPE ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.725	0.725
	PSAV_AVE[B] ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.732	0.725

A: model A B: model B
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
All c-indices were bias-corrected
Cox proportional hazard analysis with 500 times bootstrapping was utilized to get bias-corrected c-index

Part B

Model A. Prediction model for all active surveillance patients, overall progression as endpoint

Variable	HR	SE	P	95%CI
PSAV-AVE≥0.75 ng/ml/yr	1.43	0.21	0.02	1.07, 1.92
dxPOS	1.57	0.11	<0.001	1.37, 1.79
MXPT	1.02	0.004	<0.001	1.02, 1.03
PSA at diagnosis	1.01	0.02	0.56	0.97, 1.06
Bias-corrected c-index	0.702			

*cutoff of PSAV for all people 0.75 ng/ml/yr
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy, continuous variable
dxPOS: number of positive core at diagnosis in biopsy, continuous variable
Multivariate Cox proportional hazard analysis was used to get the outcomes

Model B. Prediction model for all active surveillance patients, progression by tumor volume as endpoint

Variable	HR	SE	P	95%CI
PSAV-AVE≥0.75 ng/ml/yr	1.54	0.25	0.01	1.12, 2.11
dxPOS	1.58	0.11	<0.001	1.37, 1.81
MXPT	1.03	0.004	<0.001	1.02, 1.03
PSA at diagnosis	1.00	0.03	0.91	0.97, 1.06
Bias-corrected c-index	0.732			

*cutoff of PSAV for all people 0.75 ng/ml/yr
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
Multivariate Cox proportional hazard analysis was used to get the outcomes

Table 11

Part A Subgroup analysis for 208 active surveillance patients with diagnostic PSA<4 ng/ml

Endpoint	Target PSA Kinetics	Covariate including in the prediction model	C-index	C-index w/o kinetics
Overall Progression	PSADT[C]≥4 year	age at diagnosis, PSA at diagnosis, MXPT, dxPOS	0.721	0.719
	PSAV_SLOPE ≥0.4 ng/ml/yr	age at diagnosis, PSA at diagnosis, verylow-risk cancer status	0.714	0.702
	PSAV_AVE ≥0.4 ng/ml/yr	age at diagnosis, PSA at diagnosis, verylow-risk cancer status	0.703	0.702
Progression by GS	PSADT≥4 year	age at diagnosis, PSA at diagnosis	0.716	0.688
	PSAVSLOPE[D] ≥0.4 ng/ml/yr	age at diagnosis, PSA at diagnosis	0.739	0.688
	PSAV_AVE ≥0.4 ng/ml/yr	age at diagnosis, PSA at diagnosis	0.698	0.688
Progression by TV	PSADT[E]≥4 year	age at diagnosis, PSA at diagnosis, dxPOS, MXPT, verylow-risk cancer status	0.742	0.739
	PSAV_SLOPE ≥0.4 ng/ml/yr	age at diagnosis, PSA at diagnosis, verylow-risk cancer status	0.734	0.725
	PSAV_AVE ≥0.4 ng/ml/yr	age at diagnosis, PSA at diagnosis, verylow-risk cancer status	0.723	0.725

C: model C D: model D E: model E
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
All c-indices were bias-corrected
Cox proportional hazard analysis with 500 times bootstrapping was utilized

Part B

Model C. Prediction model for 208 active surveillance patients with diagnostic PSA<4, overall progression as endpoint

Variable	HR	SE	P	95%CI
PSADT≥4 years	1.05	0.34	0.89	0.55, 1.98
PSA at diagnosis	1.52	0.24	0.01	1.12, 2.06
age at diagnosis	1.05	0.03	0.03	1.00, 1.10
MXPT	1.02	0.01	0.04	1.00, 1.05
dxPOS	1.64	0.22	<0.001	1.26, 2.14
Bias-corrected c-index	0.721			

*cutoff of PSADT is 4 years
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
Multivariate Cox proportional hazard analysis was used to get the outcomes

Model D. Prediction model for 208 active surveillance patients with diagnostic PSA<4, progression by GS as endpoint

Variable	HR	SE	P	95%CI
PSAV-SLOPE≥0.4 ng/ml/yr	2.45	1.32	0.10	0.85, 7.04
PSA at diagnosis	1.08	0.30	0.78	0.63, 1.84
age at diagnosis	1.08	0.05	0.12	0.98, 1.19
Bias-corrected c-index	0.739			

*cutoff of PSAV for people with initial diagnosis PSA<4 is 0.4 ng/ml/yr
Multivariate Cox proportional hazard analysis was used to get the outcomes

Model E. Prediction model for 208 active surveillance patients with diagnostic PSA<4, progression by tumor volume as endpoint

Variable	HR	SE	P	95%CI
PSADT≥4 years	1.25	0.48	0.56	0.59, 2.65
age at diagnosis	1.04	0.03	0.13	0.99, 1.10
very-low risk cancer	0.56	0.25	0.19	0.24, 1.33
DxPOS	1.55	0.24	<0.001	1.14, 2.11
MXPT	1.03	0.12	0.01	1.01, 1.05
PSA at diagnosis	1.72	0.30	0.002	1.22, 2.42
Bias-corrected c-index	0.742			

*cutoff of PSADT is 4 years
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
Multivariate Cox proportional hazard analysis was used to get the outcomes

Table 12

Part A Subgroup analysis for 406 active surveillance patients with diagnostic PSA≥4 ng/ml

Endpoint	Target PSA Kinetics	Covariate including in the prediction model	C-index	C-index w/o kinetics
Overall Progression	PSADT≥4 year	PSA at diagnosis, MXPT, dxPOS	0.715	0.710
	PSAV_SLOPE ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.714	0.710
	PSAV_AVE[F] ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.716	0.710
Progression by GS	PSADT≥4 year	PSA at diagnosis	0.576	0.531
	PSAV_SLOPE ≥0.75 ng/ml/yr	PSA at diagnosis	0.557	0.531
	PSAV_AVE ≥0.75 ng/ml/yr	PSA at diagnosis	0.568	0.531
Progression by TV	PSADT≥4 year	PSA at diagnosis, MXPT, dxPOS	0.747	0.744
	PSAV_SLOPE ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.747	0.744
	PSAV_AVE[G] ≥0.75 ng/ml/yr	PSA at diagnosis, MXPT, dxPOS	0.751	0.744

F: model F G: model G
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
All c-indices were bias-corrected
Cox proportional hazard analysis with 500 times bootstrapping was utilized to get bias-corrected c-index

Part B

Model F. Prediction model for 406 active surveillance patients with diagnostic PSA≥4, overall progression as endpoint

Variable	HR	SE	P	95%CI
PSAV-AVE≥0.75 ng/ml/yr	1.38	0.24	0.06	0.99, 1.94
PSA at diagnosis	0.93	0.04	0.06	0.86, 1.00
MXPT	1.02	0.005	<0.001	1.01, 1.03
dxPOS	1.49	0.12	<0.001	1.27, 1.76
Bias-corrected c-index	0.716			

*cutoff of PSAV for people with initial diagnosis PSA>4 is 0.75 ng/ml/yr
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
Multivariate Cox proportional hazard analysis was used to get the outcomes

Model G. Prediction model for 406 active surveillance patients with diagnostic PSA≥4, progression by tumor volume as endpoint

Variable	HR	SE	P	95%CI
PSAV-AVE≥0.75 ng/ml/yr	1.55	0.29	0.02	1.08, 2.24
PSA at diagnosis	0.91	0.04	0.03	0.83, 0.99
MXPT	1.03	0.01	<0.001	1.02, 1.04
dxPOS	1.48	0.13	<0.001	1.25, 1.75
Bias-corrected c-index	0.751			

*cutoff of PSAV for people with initial diagnosis PSA>4 is 0.75ng/ml/yr
MXPT: maximum percentage tumor involvement of core at diagnosis in biopsy
dxPOS: number of positive core at diagnosis in biopsy
Multivariate Cox proportional hazard analysis was used to get the outcomes

Figure 1

Kaplan-Meier curve for all 614 active surveillance patients with overall progression

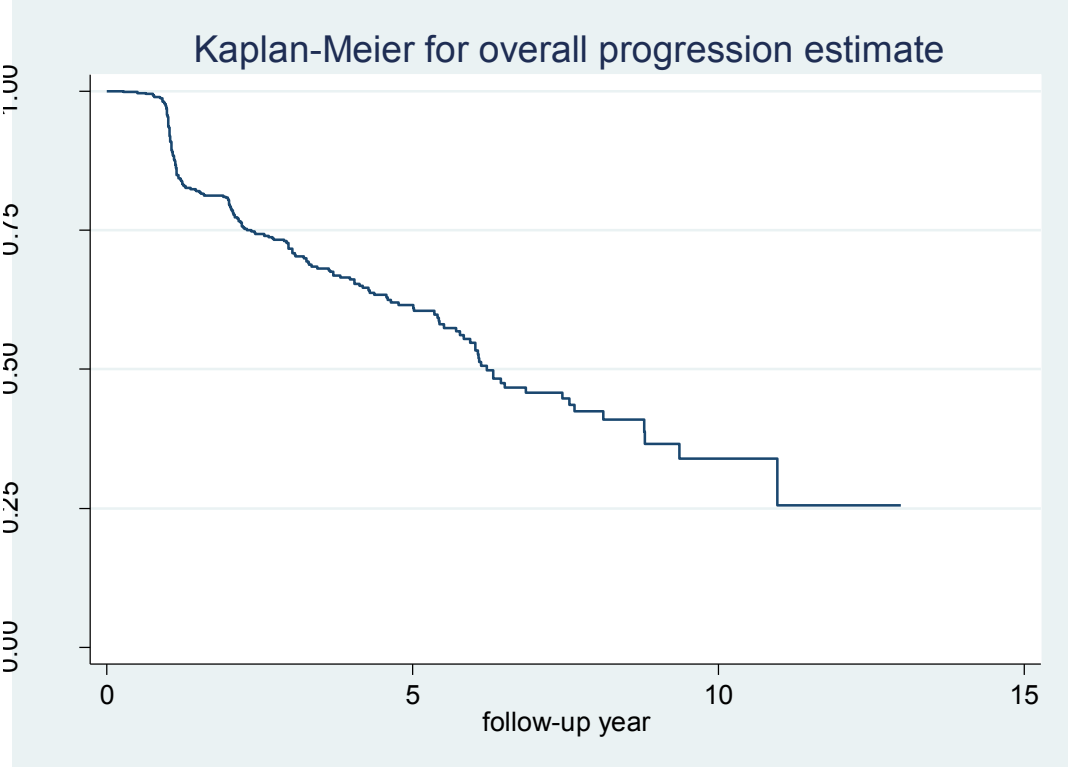


Figure 2

Kaplan-Meier curve for all 614 active surveillance patients with progression by GS

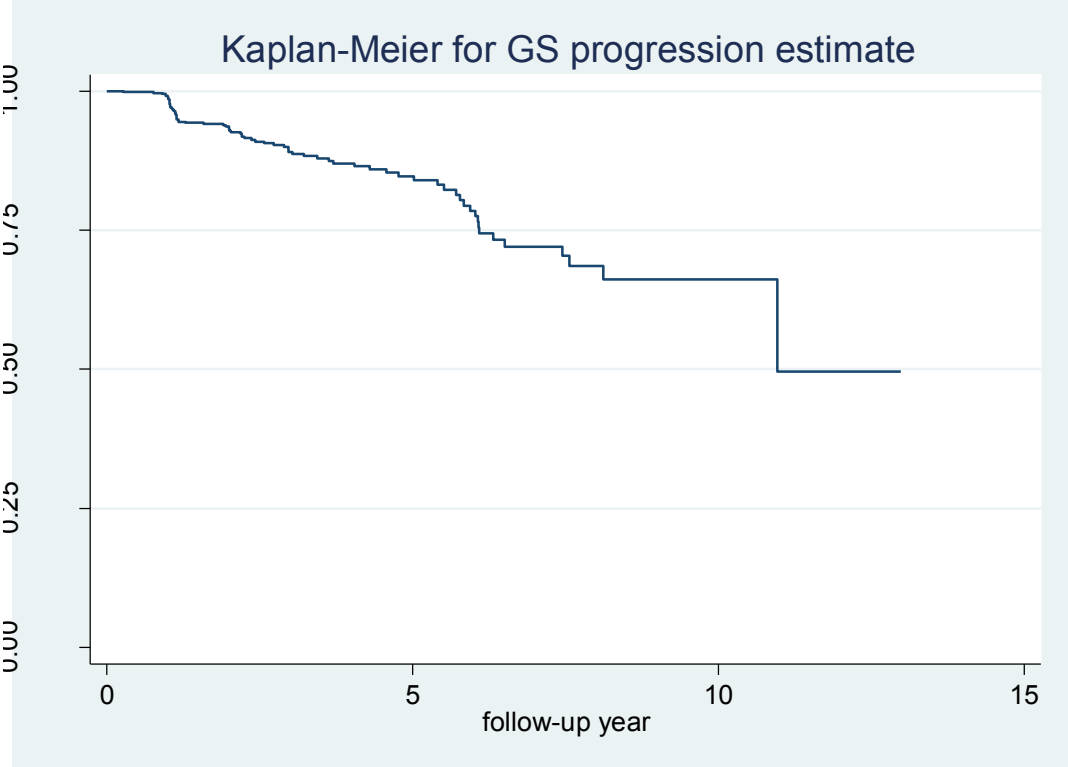


Figure 3

Kaplan-Meier curve for all 614 active surveillance patients with progression by tumor volume

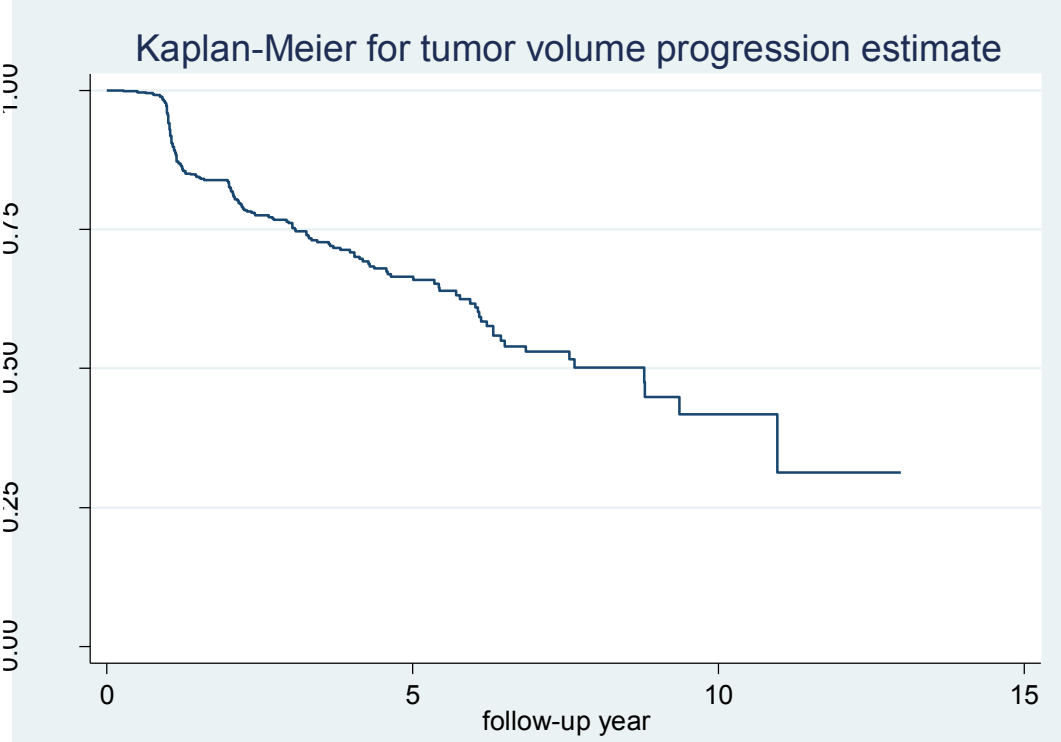


Figure 4

Boxplot for all-sample 614 active surveillance patients, compare PSA and PSA kinetics between overall progression and non-progression

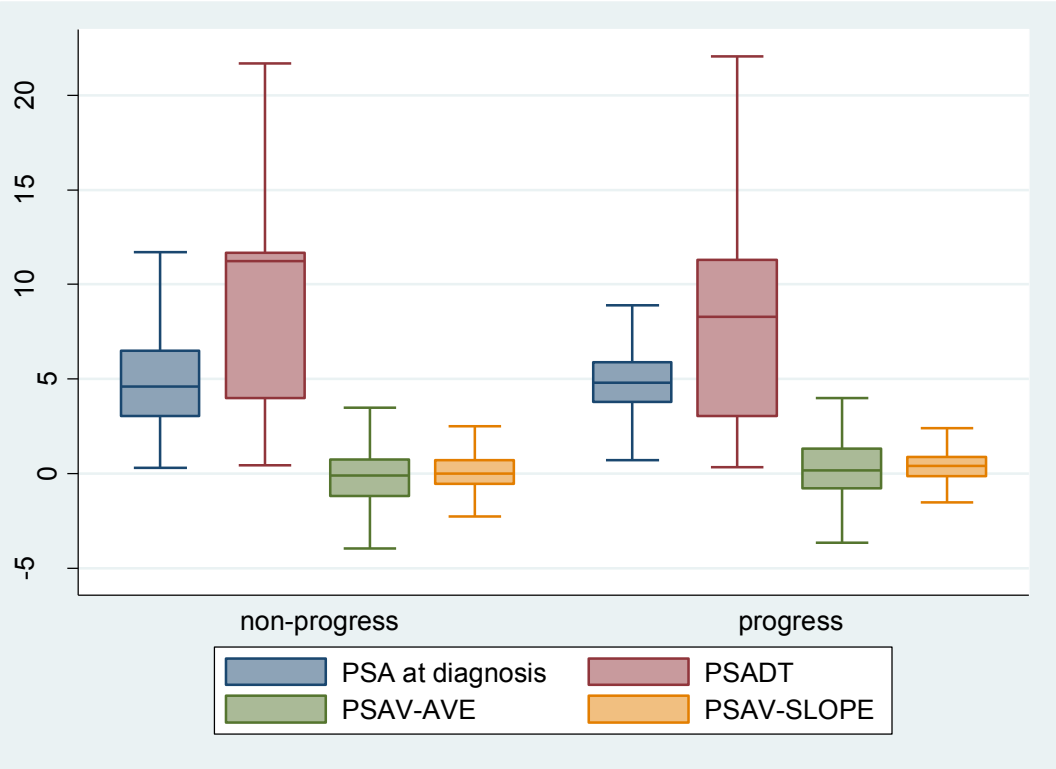


Figure 5

Boxplot for all-sample 614 active surveillance patients, compare PSA and PSA kinetics between progression by GS and non-progression by GS

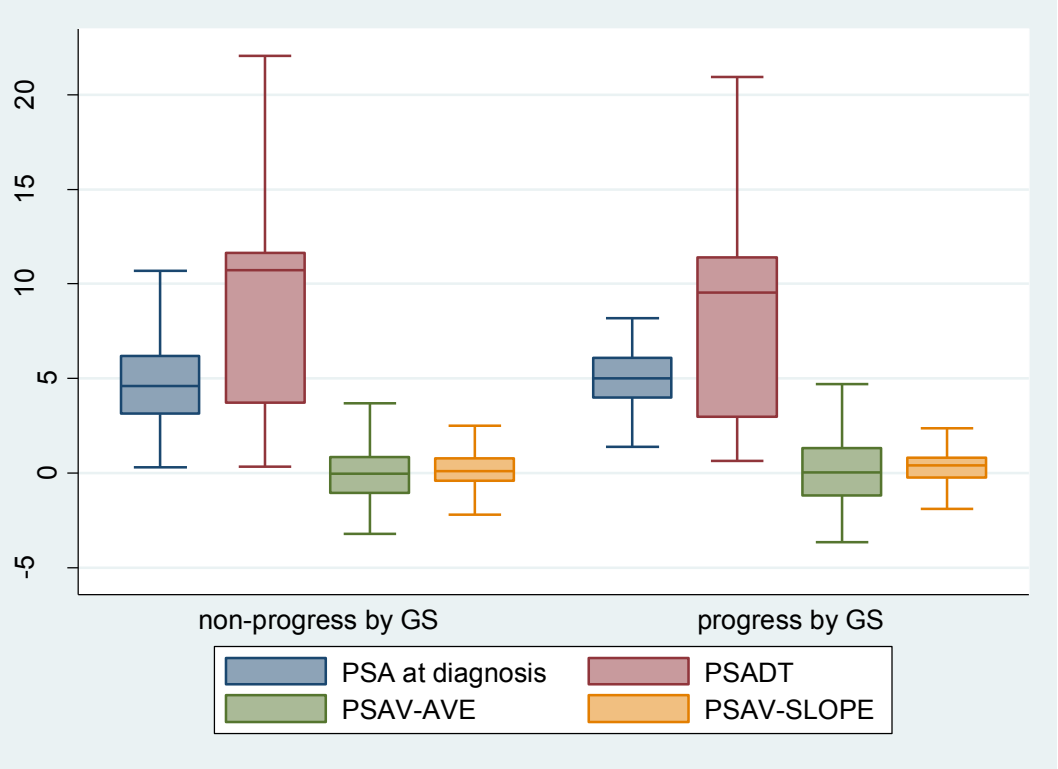


Figure 6

Boxplot for all-sample 614 active surveillance patients, compare PSA and PSA kinetics between progression by tumor volume and non-progression by tumor volume

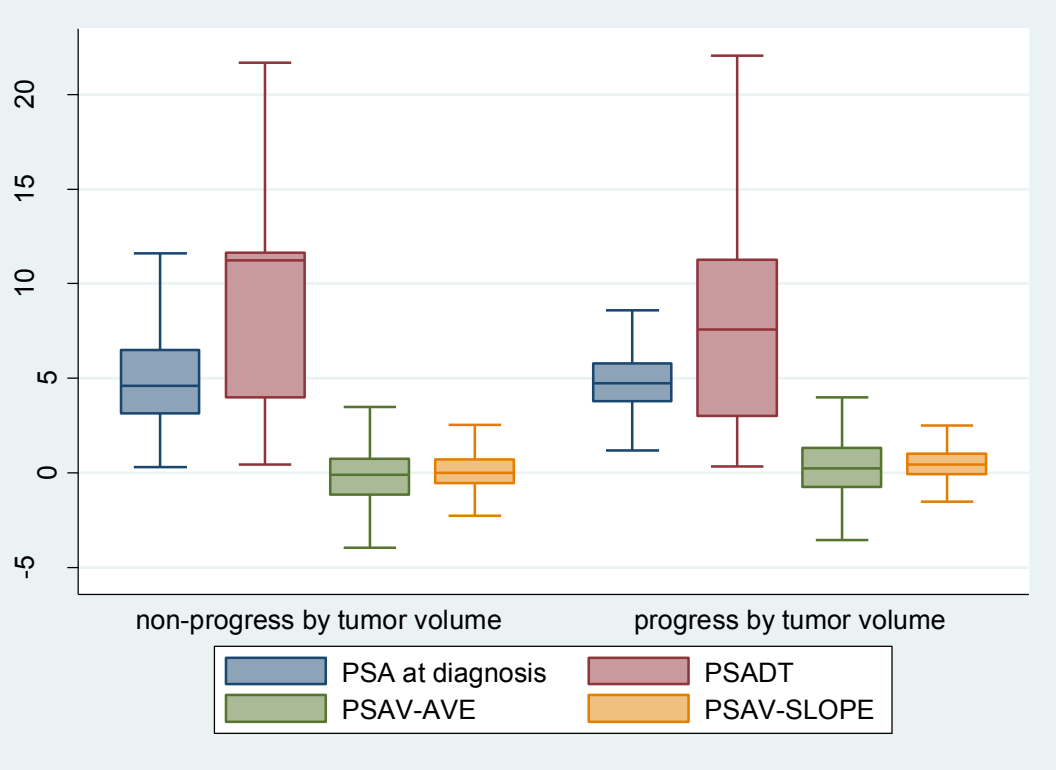


Figure 7

Boxplot for 208 active surveillance patients with diagnostic PSA<4 ng/ml, compare PSA and PSA kinetics between overall progression and non-progression

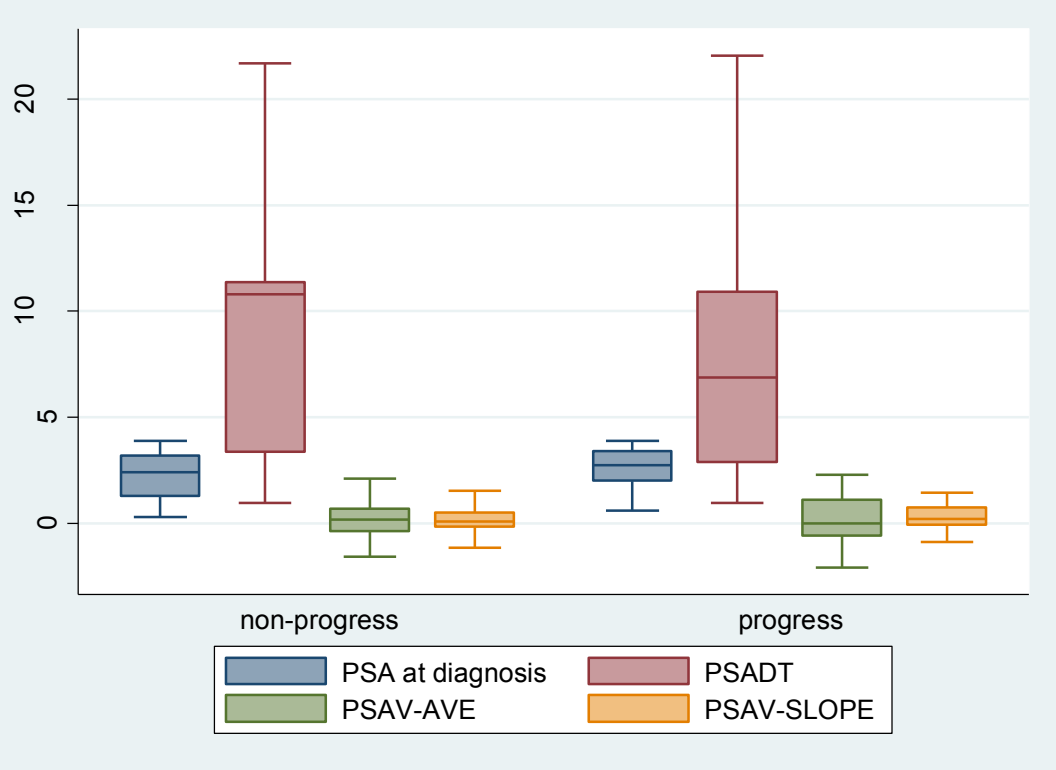


Figure 8

Boxplot for 208 active surveillance patients with diagnostic PSA<4 ng/ml, compare PSA and PSA kinetics between progression by GS and non-progression by GS

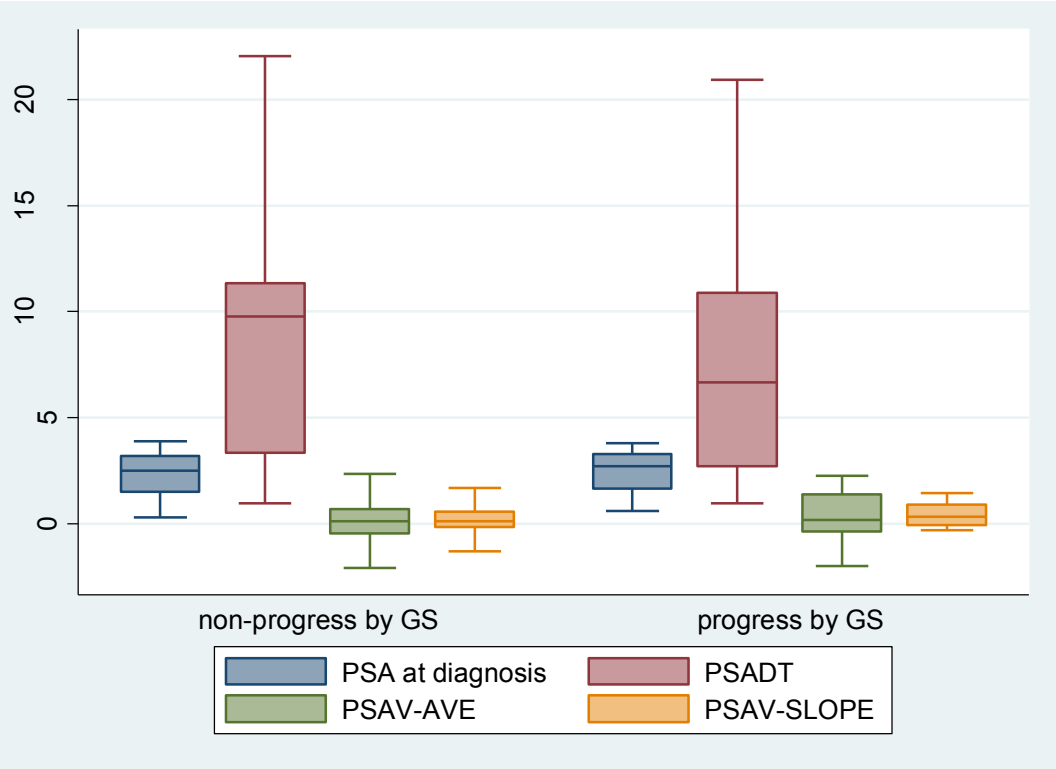


Figure 9

Boxplot for 208 active surveillance patients with diagnostic PSA<4 ng/ml, compare PSA and PSA kinetics between progression by tumor volume and non-progression by tumor volume

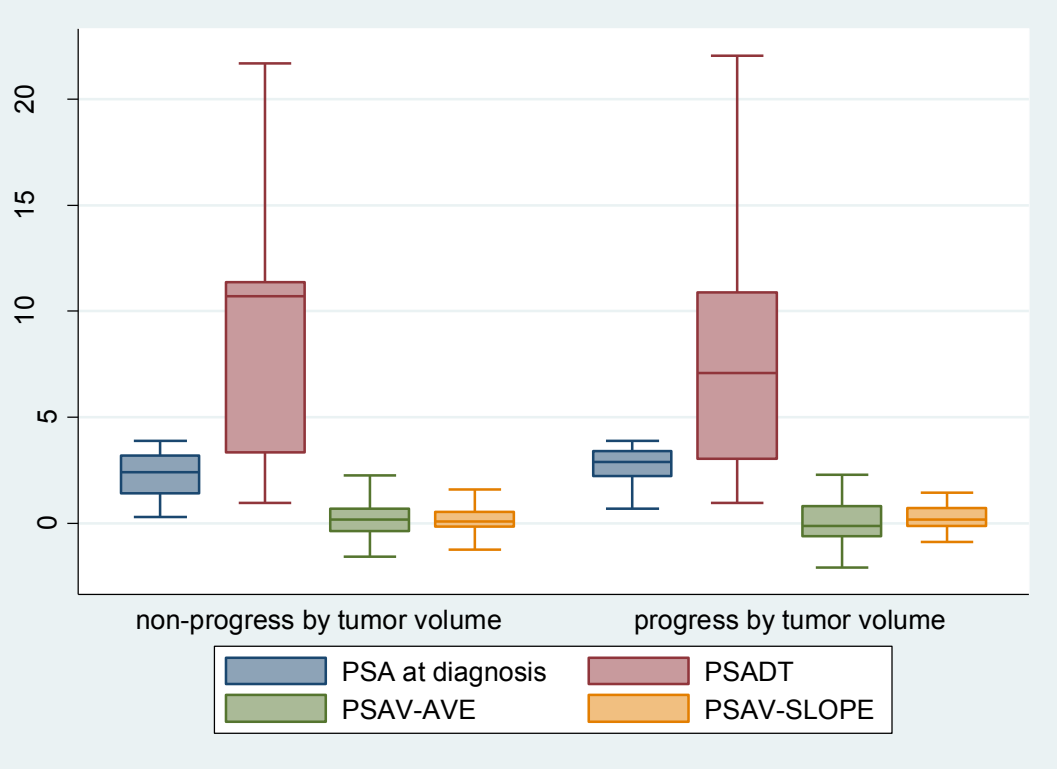


Figure 10

Boxplot for 406 active surveillance patients with diagnostic PSA≥4 ng/ml, compare PSA and PSA kinetics between overall progression and non-progression

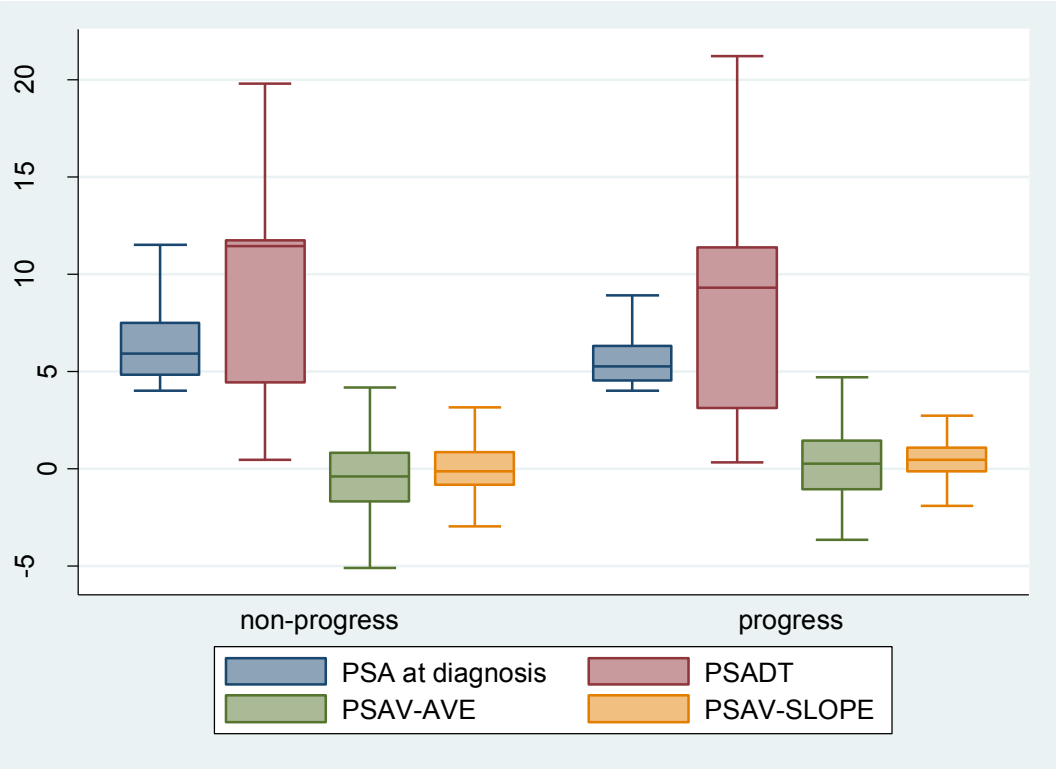


Figure 11

Boxplot for 406 active surveillance patients with diagnostic PSA≥4 ng/ml, compare PSA and PSA kinetics between progression by GS and non-progression by GS

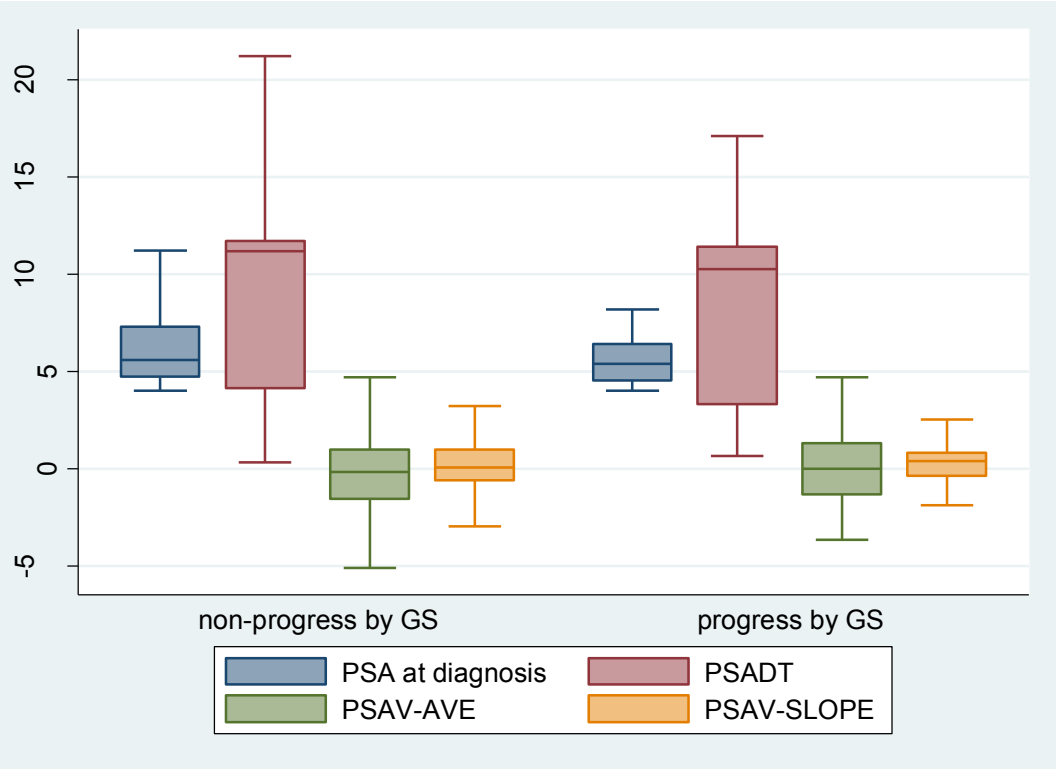
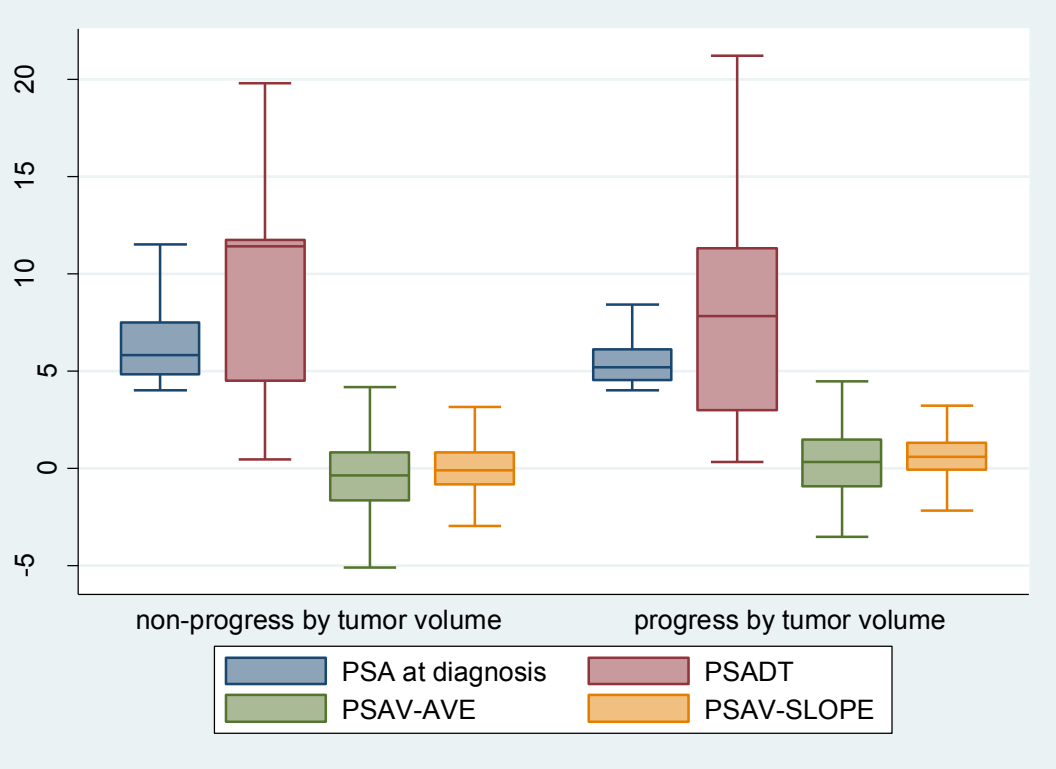


Figure 12

Boxplot for 406 active surveillance patients with diagnostic PSA≥4 ng/ml, compare PSA and PSA kinetics between progression by tumor volume and non-progression by tumor volume



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PROFILE

Dongyu Zhang, born in 1988 November 7th at Chengdu in China, acquired the master of science (ScM) in epidemiology at Johns Hopkins University Bloomberg School of Public Health with additional training in cancer etiology and prevention, clinic oncology,environmental/occupational health, clinic trial and systematic review. Strong background in clinic medicine and public health practice. Research areas include prognosis biomarker for cancer and systematic review for cancer and eye disease. Fluent in English and Chinese.

EDUCATION

Master of Science (ScM) in Epidemiology May 2014
Johns Hopkins Bloomberg School of Public Health, Baltimore MD
Relevant Coursework: Epidemiology method series; Biostatistics series; Systematic review; Cancer etiology and prevention; Clinic oncology; GIS and spatial analysis; Clinic trial data management; Environmental/Occupation health; Cardiovascular/obesity/diabetes epidemiology

Certificate in Environmental and Occupational Health Dec 2013
Johns Hopkins Bloomberg School of Public Health, Baltimore MD

Bachelor of Medicine in Preventive Medicine June 2012
Sichuan University, Chengdu China

CLINIC/PUBLIC HEALTH EXPERIENCE

Intern Physician Aug 2010-Jan 2011
West China Hospital, Chengdu, China
• Made examination, diagnosis and prescription for patients
• Served as surgery assistant
• Managed medical history from patients
• Served as assistant for emergency medical issue

Intern Jul 2011-Aug 2011
Center for Disease Control in Wuhou District, Chengdu, China
• Managed medical record for HIV patients
• Prescribed antiretroviral drug for HIV patients
• Conducted epidemiological survey for infectious disease
• Analyzed data from community-based health surveillance for chronic disease

RESEARCH EXPERIENCE

Dissertation Researcher Jun 2013-Apr 2014
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
• Study design for research discussing about prostate cancer kinetics
• Performed statistical analysis
• Academic issue/outcome discussion with advisor
• Drafting manuscript

Research Assistant Feb 2014-May 2014
The Johns Hopkins Center for Clinical Trials, Baltimore, MD
Project:
Antiviral treatment and other therapeutic interventions for herpes simplex virus epithelial keratitis;
Comprehensive research on literature citation about eye diseases
• Performed publication retrieving from different databases
• Performed data extraction and publication review for Cochrane Eyes and Vision Group
• Discussed academic issue/outcome with team members

Research Assistant Oct 2013-Jan 2014
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Project: Cochrane Eyes and Vision Group's research: device modified trabeculectomy for glaucoma
• Performed data extraction and publication review for Cochrane Eyes and Vision Group
• Discussed academic issue/outcome with team members

Research Assistant Mar 2013-Aug 2013
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Project: Prognostic value of CIMP in patients with colorectal cancer
• Performed title/abstract screening for systematic review about colorectal cancer
• Performed data extraction and publication review
• Discussed academic issues/outcomes with team members
• Revised manuscripts

Research Assistant Apr 2011–May 2012
West China Hospital, Chengdu, China
Project: The role of palliative chemotherapy for terminal ill patients with advanced NSCLC
• Designed study for research discussing about palliative chemotherapy for lung cancer
• Performed statistical analysis
• Revised manuscripts

Project Leader Apr 2011-May 2012
Sichuan University, Chengdu, China
Project: Exploration research on senile depression
• Grand application and study design for research about depression
• Performed data collection and statistical analysis
• Outcome presentation and report writing

TEACHING EXPERIENCE
Teaching Assistant Sept 2013-Dec 2013
Johns Hopkins Bloomberg School of Public Health, Baltimore, MD
Course: Principle of epidemiology; Observational epidemiology
• Taught in lab session and held office hours for entry-level epidemiology course
• Graded students' assignments/exams and guided them in lecture and exam preparation
• Attended instructors' meetings

PUBLICATION

Yen-Yi Juo; Fabian Johnston; **Dongyu Zhang**; Hsin-Hsuan Juo; Han Wang; Emmanouil P. Pappou; Tsung Yu; Nita Ahuja. Prognostic Value of CpG Island Methylator Phenotype among Colorectal Cancer Patients: A Systematic Review and Meta-Analysis. Annals of Oncology 00: 1–15, 2014 doi: 10. 1093/annonc/mdu149

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