Predicting metastatic disease progression in prostate cancer patients using machine learning of PSA kinetics

Green F., Rioth M. MD, Lorenzo R., Loving J. PhD
Syapse, San Francisco, CA

Syapse®
ISPOR 2023
May 7-10, 2023
Poster ID: RWD55
Abstract Number: 126852

OBJECTIVES

Although only 5% of patients with prostate cancer (PCA) have metastases at diagnosis, approximately 20% of those with early-stage disease experience recurrence with metastases, often years later.[1,2] Changes in prostate specific antigen (PSA) levels can predict recurrence. In this study, we aimed to develop a machine learning model that can effectively predict metastatic progression in PCA patients based on serum PSA lab kinetics after the initial diagnosis of localized PCA. By utilizing longitudinal data on PSA levels and other relevant clinical features, we sought to create a robust predictive model that could provide valuable information for clinicians and improve patient outcomes. Our model aimed to predict metastatic events 1.5 years before their clinical detection, allowing for earlier intervention and more effective management of PCA patients. This machine learning approach has the potential to help clinicians make more informed decisions regarding patient care and treatment planning.

METHODS

In this study, PSA lab values for 4,654 prostate cancer (PCA) patients, including 4,321 non-metastatic and 333 metastatic cases, were evaluated. The data comprised patients without metastases at diagnosis. The lab values were considered starting from the time of diagnosis up to an observation cutoff of 3.5 years for surviving patients, with subsequent lab visits being censored. To establish lead time in patients with metastases, labs were withheld for 1.5 years before the appearance of metastases. Patients with normal PSA levels at diagnosis were also included in the study.

For the selection and balancing process, a patient funnel was created, which involved stratifying the initial cohort of PCA patients meeting observation constraints into non-metastatic and metastatic groups. Bootstrapping was then applied to non-metastatic patients before training to create equally-weighted metastatic status labels, followed by a 70:30 train-test split for model testing.

A binary classification model using the XGBoost algorithm was developed, with aggregated PSA levels and other clinical and laboratory attributes serving as feature inputs. These attributes included visit count during the observation period, aggregated descriptive statistics of both patient PSA values and velocity of PSA levels with variable visit gap length, count of visit delays of 6 months or greater, and count of rising PSA levels across three or more visits. Model selection was determined by tuning the observation period constraints.

RESULTS

Our classifier, trained on bootstrapped samples of the non-metastatic population, achieved a mean test accuracy of 0.74 (SD = 0.03, max = 0.79), precision of 0.74 (SD = 0.05, max = 0.82), and sensitivity of 0.75 (SD = 0.05, max = 0.84) across 20 iterations. The mean F1 score across the iterations was 0.74 (SD = 0.04, max = 0.80), indicating a balanced performance in terms of precision and recall. The model utilized a maximum of 3.5 years of observed lab values and aimed to predict metastasis events 1.5 years before their clinical detection.

The observation cutoff and lead time constraints were critical in focusing the model on relevant data and ensuring reliable predictions within the specified time frame. The model's performance may be affected by the relationship between the observation cutoff and lead time, as it relies on a limited window of lab values to predict metastasis events. Our classifier demonstrates promising performance, with a strong emphasis on the time-dependency of longitudinal PSA values across patient visits. In addition to PSA values, the model input included feature engineering of patient-level PSA kinetics respective to sequential lab values and visit gap lengths, as well as aggregated descriptive statistics of patient PSA values, extended visit delays, and instances of rising PSA levels. The inclusion of these relevant features contributes to the robustness of the model's predictions, effectively capturing the complex dynamics of prostate cancer progression and metastasis prediction.

CONCLUSIONS

The machine learning approach presented in this study demonstrates the potential for using longitudinal PSA kinetics to forecast the appearance of metastases in patients diagnosed with early-stage PCA, years in advance. The model achieved a mean test accuracy, precision, and sensitivity comparable to other methods predicting PCA recurrence using PSA kinetics, but with a clinically-relevant lead time of 1.5 years before clinical detection. This lead time allows for earlier intervention and more effective management of PCA patients, ultimately improving patient outcomes.

By incorporating the observation cutoff and lead time constraints used in this study with other clinical and laboratory features, the model focuses on relevant data, enhancing the reliability of its predictions.

With further development and validation, accurate prediction of disease progression may be applied not only to PCA but also to other malignancies, with the goal of improving patient outcomes and informing clinical decision-making for patient care and treatment planning.

REFERENCES

1. Eur Urol. 2022 Feb;81(2):184-192.
2. Litwin MS, Tan HJ. The Diagnosis and Treatment of Prostate Cancer: A Review. JAMA. 2017 Jun 27;317(24):2532-2542.

FIGURE 1. Representative patient visits **(circles)** are shaded to illustrate observation constraints, green for inclusion and grey for exclusion. **(1)** 3.5-year maximum from index cancer diagnosis **(orange triangle)**, excluding pre-cancer visits; **(2)** grey-shaded region denoting 1.5-year lead time censoring from metastasis event **(red triangle)**, with prediction **(star)** at lead time origin; **(3)** maintained 1.5-year censoring if metastasis occurs within 3.5 years of index; **(4)** inclusion of patients with last recorded visit or mortality **(square)** before observation cutoff

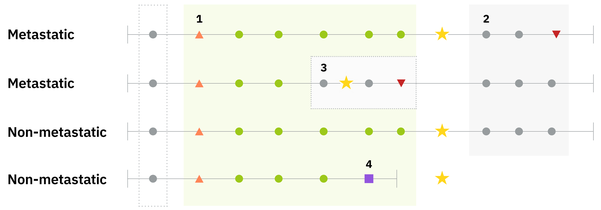

FIGURE 2. Patient funnel illustrating selection and balancing process: The initial cohort consists of 4,654 prostate cancer patients meeting observation constraints, stratified into 4,321 non-metastatic and 333 metastatic patients. Bootstrapping is then applied to non-metastatic patients to create an equal-sized balanced cohort (333 patients each), followed by a 70:30 train-test split for model development and evaluation.

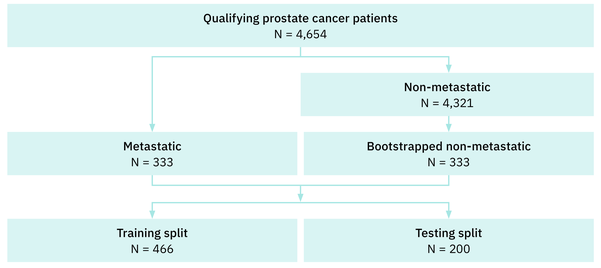

TABLE 1 Summary statistics of model performance metrics from 20 bootstrapped rounds of the non-metastatic group, illustrating variability and reliability across different training subsets.

	PPV	NPV	TPR	TNR	FPR	FNR	FDR	F1	Accuracy
mean	0.74	0.75	0.75	0.74	0.26	0.25	0.26	0.74	0.74
std	0.05	0.04	0.05	0.05	0.05	0.05	0.05	0.04	0.03
min	0.65	0.67	0.67	0.66	0.17	0.16	0.18	0.67	0.68
25%	0.71	0.72	0.71	0.7	0.23	0.21	0.24	0.71	0.72
50%	0.74	0.75	0.74	0.72	0.28	0.26	0.26	0.74	0.75
75%	0.76	0.77	0.79	0.77	0.3	0.29	0.29	0.77	0.76
max	0.82	0.83	0.84	0.83	0.34	0.33	0.35	0.8	0.79

FIGURE 3 ROC curve for the predictive model, demonstrating high discriminatory performance with an AUC of 0.97, indicating its effectiveness in distinguishing between metastatic and non-metastatic prostate cancer patients.

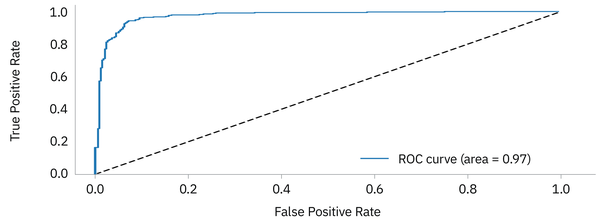

FIGURE 4 Longitudinal patient visit sequences connected by lines, displaying normalized PSA values (y-axis) and time elapsed since cancer diagnosis (x-axis, up to 3.5-year observation cutoff).