



## Research Article

## Prostate cancer trajectory-map: clinical decision support system for prognosis management of radical prostatectomy

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## ABSTRACT

**Purpose:** Prostate cancer has a low mortality rate and requires persistent treatment; however, treatment decisions are challenging. Because prostate cancer is complex, the outcomes warrant thorough follow-up evaluation for appropriate treatment. Electronic health records (EHRs) do not present intuitive information. This study aimed to develop a Clinical Decision Support System (CDSS) for prognosis management of radical prostatectomy.

**Methods:** We used data from 5,199 prostate cancer patients from three hospitals' EHRs in South Korea, comprising laboratory results, surgery, medication, and radiation therapy. We used open source R for data preprocessing and development of web-based visualization system. We also used R for automatic calculation functionalities of two factors to visualize the data, e.g., Prostate-Specific Antigen Doubling Time (PSADT), and four Biochemical Recurrence (BCR) definitions: American Society of Therapeutic Radiology and Oncology (ASTRO), Phoenix, consecutive PSA > 0.2 ng/mL, and PSA > 0.2 ng/mL.

**Results:** We developed the Prostate Cancer Trajectory Map (PCT-Map) as a CDSS for intuitive visualization of serial data of PSA, testosterone, surgery, medication, radiation therapy, BCR, and PSADT.

**Conclusions:** The PCT-Map comprises functionalities for BCR and PSADT and calculates and visualizes the newly added patient data automatically in a PCT-Map data format, thus optimizing the visualization of patient data and allowing clinicians to promptly access patient data to decide the appropriate treatment.

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## 1. Introduction

With the development of radical prostatectomy, including robotic surgery, the mortality rates among prostate cancer patients and the requirement of persistent treatment have decreased.<sup>1-3</sup> However, treatment decisions for prostate cancer are not simple, because prostate cancer is a complex disease and pathological opinions differ among pathologists. Hence, clinicians are considering various laboratory test results such as prostate-specific

antigen (PSA) blood test and biopsy.<sup>4,5</sup> The PSA blood test helps determine the risk of prostate cancer leading to early detection and reduced mortality.<sup>4,5</sup> Based on serial PSA blood test results, biochemical recurrence (BCR) has been considered to identify patients with early treatment failure.<sup>6,7</sup> Furthermore, ultrasensitive monitoring of PSA kinetics is an important method to identify patients requiring additional treatment.<sup>8</sup>

BCR is an important criterion for early treatment because of the long lifespan of prostate cancer patients.<sup>1</sup> Although BCR is useful, it is time-consuming to identify early treatment failure in accordance with it. We need computerized support to approach clinical decisions to minimize human effort. Automated systems can be used to determine recurrence by reducing time and effort, rather than querying individual patient data to determine the BCR. Kawamoto, et al (2005) suggested four features to successfully

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establish a clinical decision support system (CDSS), including the following: (1) automatic provision of decision support as part of clinical protocols; (2) real-time provision of decision support during decision making; (3) provision of recommendations rather than just an assessment; and (4) computer-based provision of decision support.<sup>9</sup> Based on the aforementioned four characteristics of the successful CDSS, we developed the Prostate Cancer Trajectory Map (PCT-Map) for clinicians for better prognosis management for patients undergoing radical prostatectomy.

## 2. Materials and methods

### 2.1. Materials

Three university hospitals located in Seoul, South Korea were included in the study. We obtained data from 5,198 anonymized patients of prostate cancer after radical prostatectomy: lot consisting of 1,698 patients from hospital C, 2,432 from hospital S, and 1,068 from hospital A. This study was approved by the institutional review boards of the respective participating institutes. The data comprised several temporal clinical records including laboratory results, surgery, medication, and treatment.

In this study, we used the standard format of Asia prostate cancer (A-CaP) study.<sup>10</sup> The A-CaP study started in 2015 and has held annual symposium. The A-CaP study has two objectives. First was to clarify the clinical situation of prostate cancer (PCa). Second was to use the outcomes for international comparison. Because all three hospitals in this study had also joined the A-CaP study, we could obtain the A-CaP standard data which are available to implement the same system for different hospitals.

We assessed several factors to visualize the data from electronic medical records (EMRs). First, PSA analysis was performed to understand the underlying kinetics and determine the BCR time-point and PSA doubling time (PSADT). Furthermore, we assessed the results of testosterone quantification, laboratory tests, medication, surgery, and radiation therapy. BCR was used to assess treatment outcomes, which indicates the failure rate. PSADT is an important factor we used in decision making in treating prostate cancer, e.g., metastatic disease.<sup>11</sup>

In case of medication, commonly used treatment agents for prostate cancer were determined, including pharmacotherapeutic drugs, bilateral orchiectomy for surgical castration, goserelin (Zoladex, brand name), leuprolide (Lupron Deepot, brand name), and triptorelin (Trelstar, brand name) as Luteinizing-hormone Releasing Hormone (LHRH) agonist, degarelix as LHRH antagonist, nilutamide (Nilandron), flutamide (Eulexin), bicalutamide (Casodex), ketoconazole (Nizoral), enzalutamide (Xtandi), abiraterone (Zytiga), apalutamide (Erleada), and olaparib as first-generation antiandrogens, and docetaxel (Taxotere) and cabazitaxel (Jevtana) for chemotherapy (CTx).

In cases of surgery, the PCT-map included the surgery date and surgery terminology.

Because of the security reason, we stratified age into several groups in 5 years. It is based on hospitals' security policy which restricts age must be stratified to avoid the possibilities of identifying individuals.

### 2.2. Ethics

The PCT-Map procedure was carried out in accordance with the Declaration of Helsinki and was approved by the respective Institutional Review Boards (IRBs) of Hospital C (IRB number: KC18SNDI0512), Hospital S (IRB number: SMC201807069001), and Hospital A (IRB number: 2018-0963). Each data management department deidentified and formatted the data from the EMRs.

Unless locally managed mapping data were exposed, no patients could be identified in particular.

### 2.3. Methods

Herein, we used four BCR definitions based on the American Urological Association Prostate Guidelines for Localized Prostate Cancer Update Panel Report and Recommendations for a Standard in the Reporting of Surgical Outcomes.<sup>6</sup>

Details regarding BCR are as follows. The American Society of Therapeutic Radiology and Oncology (ASTRO) involves three consecutive increases in PSA after nadir has been reached, with the date of failure being the midpoint between the nadir and the first of 3 consecutive increases.<sup>6</sup> According to the Phoenix definition, BCR is an increase of at least 2.0 ng/mL from nadir PSA.<sup>12</sup> The third definition involves two consecutive PSA values > 0.2 ng/mL following prostatectomy.<sup>6</sup> The last definition involves a PSA cut-off point value > 0.2 ng/mL after radical prostatectomy.<sup>6</sup> Herein, we developed BCR calculation functionality for all four BCR definitions.

PSA doubling time (PSADT) is an important value that potentially predicts metastatic disease progression.<sup>11</sup> Numerous studies have attempted to determine the PSADT.<sup>11,13-16</sup> Doubling time (DT) indicates an exponential growth phase of certain specific objects., we used the definition of Pound CR. et al (1999) to determine the PSADT for each patient. We used a natural logarithm formula to determine the PSADT values for each patient (Eq. 1).

*Equation 1* Prostate Specific Antigen Doubling Time (PSADT) Calculation

$$y = ae^{bx}$$

$$y = 1, x1 = \frac{\ln\left(\frac{1}{a}\right)}{b}$$

$$y = 2, x2 = \frac{\ln\left(\frac{2}{a}\right)}{b} \quad (1)$$

$$Td = x2 - x1 = \frac{(\ln 2 - \ln a) - (\ln 1 - \ln a)}{b}$$

$$Td = \frac{\ln 2}{b}$$

where

*y* = log scaled PSA values  
*x* = PSA test time(days)  
*x1* = PSA test start time  
*x2* = PSA test doubled time  
*Td* = Doubling Time

For the visualization functionality, we developed front-end and back-end services using the R shiny package<sup>17</sup>, open-source software for development. The front-end is a web-based user interface. Clinicians access the PCT-Map using web browsers including Chrome, Safari, Mozilla Firefox, and Internet Explorer. back-end is the engine of the PCT-Map. The back-end has several important functionalities, like BCR calculation and PSADT calculation. We developed R script functions for BCR on the basis of four BCR definitions. Furthermore, we developed R script functions for PSADT calculation on the basis of PSADT Eq. 1. We linked R script functions and the web user interface using R packages.

We developed the user interface using R (ver. 3.5.0)<sup>18</sup> and R Shiny (ver.1.2.0).<sup>17</sup> We visualized clinical data using R packages including ggplot2 (ver.3.1.0)<sup>19</sup> and plotly (ver.4.8.0).<sup>20</sup> We used R

packages snowfall (ver.1.84-6.1)<sup>21</sup> and snow (ver.0.4-3)<sup>22</sup> to develop parallel preprocessing functionalities.

The PCT-Map was developed to assist clinicians attending to outpatients, who promptly require accurate data at the appropriate time point to obtain all data. PCT-Map visualization and calculations were reviewed by clinicians. Medical informatics experts reviewed the calculation functions.

**3. Results**

We obtained anonymized data between 2007 and 2017 from prostate cancer patients admitted to three university hospitals to examine the applicability of the PCT-Map (Table 1). Data preprocessing was carried out owing to individual clinical data of numerous patients. We developed parallel preprocessing functionalities to optimize the preprocessing time. Eventually, the PCT-Map preprocessed the raw data, which had come from each of the hospitals' EMRs, within a few seconds. Unless any modifications were required in the data, the PCT-Map only carried out initial preprocessing.

Throughout the treatment, we serially assessed blood PSA data on the dashboard in the line plot. The PCT-Map visualized PSA kinetics, initial PSA, PSADT, surgery date, radiation therapy date, medication, and BCR. Because the dashboard contains the entire treatment data on one page with an intuitive visualization format, clinicians could access the data they desired instead of searching textual data from the EMR database (Fig. 1).

The PCT-Map visualized previous data and recent laboratory and treatment data to present useful information regarding prostate cancer. The PCT-Map was used to determine and visualize the newly added recent patient data instantaneously and to generate accurate data promptly. For instance, PSADT calculations were

carried out using the back-end functions of the PCT-Map. PSADT values include the doubling time (months) values atop the primary plot along with grey transparent boxes (Fig. 1) indicating increased PSA kinetics. Without the PCT-Map, clinicians need to determine the PSADT, which is time-consuming if it were to be done manually. The surgery date and description were displayed along with the PSA line plot. Information regarding surgery helps understand treatment protocols, e.g., the starting point for preoperative and postoperative treatment. Furthermore, the date of radiation therapy (RT) and description were displayed along with the PSA line plot. RT data help understand the changes in PSA kinetics. We visualized the data regarding medication, wherein the rectangular dots represented the date and description in the middle horizontal area of the visualization. The clinician could access the medication history immediately without retrieving it from the original EMR database.

The PCT-Map presents intuitive data in one screen, thus helping clinicians and reducing wasted time. For instance, Fig. 1 shows follow-up data read by a clinician in real-time. Fig. 1 illustrates the case of a patient who underwent radical prostatectomy on October 22, 2010, and adjuvant radiation therapy from December 03, 2010, to January 21, 2011. He had been under observation until October 31, 2017. According to BCR definitions 1 and 2, he experienced biochemical recurrence; however, he did not visit the hospital since then. He revisited the hospital on June 05, 2013, when his PSA levels were 10.35 ng/mL. He received maximal androgen blockade with leuprorelin and bicalutamide. During androgen deprivation therapy, his PSA doubling time shortened, which may serve as a marker for treatment failure. Two years later, his PSA levels increased even after antiandrogen withdrawal, and his medication were changed. He was diagnosed with castration-resistant prostate cancer (CRPC) and received docetaxel chemotherapy. Six months later, his PSA

**Table 1**  
Demographic data – clinical data from multiple organizations.

Organization	A	S	C
Number of patients (5,198)	1,068	2,432	1,698
Age at diagnosis (%)			
<40	2 (0.2)	0 (0.0)	2 (0.1)
40–44	5 (0.5)	0 (0.0)	3 (0.2)
45–49	12 (1.1)	6 (0.2)	18 (1.1)
50–54	48 (4.5)	99 (4.1)	59 (3.5)
55–59	141 (13.2)	331 (13.6)	178 (10.5)
60–64	245 (22.9)	614 (25.2)	346 (20.4)
65–69	260 (24.3)	685 (28.2)	495 (29.1)
70–74	256 (24.0)	590 (24.3)	437 (25.7)
75–80	97 (9.1)	107 (4.4)	155 (9.1)
80–84	2 (0.2)	0 (0.0)	5 (0.3)
initial PSA value (mean (sd*))	7.66 (7.56)	8.67 (10.06)	14.11 (47.78)
Gleason Scores (%)			
Low (3 + 3 or less)	374 (35.0)	463 (19.0)	608 (35.8)
Favorable intermediate (7 = 3 + 4)	353 (33.1)	1126 (46.3)	435 (25.6)
Unfavorable intermediate (7 = 4 + 3)	129 (12.1)	399 (16.4)	323 (19.0)
High (4 + 4 or greater)	212 (19.9)	444 (18.3)	332 (19.5)
T-stage (%)			
T1A	5 (0.5)	2 (0.1)	8 (0.5)
T1C	2 (0.2)	0 (0.0)	3 (0.2)
T2A	649 (60.8)	334 (13.7)	268 (15.8)
T2B	22 (2.1)	8 (0.3)	64 (3.8)
T2C	87 (8.1)	1254 (51.6)	778 (45.8)
T3A	219 (20.5)	547 (22.5)	358 (21.1)
T3B	64 (6.0)	281 (11.6)	201 (11.8)
T3C	1 (0.1)	0 (0.0)	1 (0.1)
T4	19 (1.8)	6 (0.2)	17 (1.0)
N-stage = N1 (%)	7 (0.7)	65 (2.7)	71 (4.2)
M-stage = M1 (%)	3 (0.3)	1 (0.0)	3 (0.2)

sd\*: standard deviation.



**Fig. 1.** The PCT-Map web-based user interface screenshot (Subject ID is hidden for security reasons): Prostate-specific antigen (PSA), PSA doubling time (PSADT), testosterone, surgery, medication, radiation therapy, and biochemical recurrence visualization.

level increased despite docetaxel chemotherapy, and enzalutamide was prescribed. After an initial short treatment response, he presented with disease progression.

The PCT-Map has web user interface has search and labeling functions, which is harnessed by clinicians and researchers for statistical analysis or machine learning approaches (Fig. 1). While reviewing the patient's treatment history using the PCT-Map, labels would be recorded via the check-box interface and comment text box, i.e., BCR and CRPC for analysis. The labeling data are present on the PCT-Map server for future use.

#### 4. Discussion

This study describes the development of the PCT-Map for prognosis management of radical prostatectomy.

We found initial PSA values difference between three hospitals (Table 1). Though there were differences, we only can get wild guess that some hospitals used to have surgery for the more severe clinically staged patients. However, initial PSA values came from not only the hospitals' laboratory but also from other small clinics or other hospitals. That is why it showed variations between three hospitals.

The results indicate that a major CDSS for prostate cancer is the Prostate Cancer Outlook Visualization System (PCOV). The PCOV CDSS projects probable outcomes after CyberKnife treatment (CyberKnife is a brand name for a device that delivers stereotactic body radiation therapy (SBRT). It's a form of external beam radiation. It can be used to treat prostate cancer and other types of cancer. Although it contains the word "knife" and is sometimes referred to as "radiosurgery," there's no knife or incision). The CDSS compares between the data of new and existing patients, including over 500 disease outcomes, and visualizes the likely outcome among the new patient data.<sup>23</sup> We generated the PCT-Map as a universal visualization system using data from 5,198 patients from three hospitals. Lin et al developed a real-time clinical decision support system comprising numerous data, including PSA, TNM stage, Gleason scores, and risk evaluation.<sup>24</sup> Previous studies have shown each of these data in each user interface, e.g., serial PSA

visualization in specific PSA-level user interfaces. The PCT-Map consolidates and visualizes follow-up data including PSA, DT, medication, and RT in one window. Therefore, clinicians can access consolidated information at a glance. Another study has attempted to generate a data-driven pathway for CRPC.<sup>25</sup> Previous studies have used PSA and hormone analyses and determined the DT for pathway identification. In addition to PSA and hormone analysis and DT, we determined the BCR point to include useful information for clinicians. The PCT-Map presents not only BCR but also further data including individual medication and treatment along with the entire follow-up timeline of patients.

Because, the PCT-Map aimed to present visualization of follow-up information of PCa patients, it showed instant visualization from serial data of text format. The PCT-Map did not capture every patient's calculated information, instead it generates visual information from instant calculation results. Though the PCT-Map shows instant information, the calculation functionalities, such as BCR or PSADT, can be used to collect aggregated information from participant hospitals.

The PCT-Map has three advantages. First, we developed real-time visualization functionalities, e.g., when clinicians access specific patient data, the PCT-Map shows not only the past history but also the recent laboratory findings and treatment data. We developed and implemented a parallel preprocessing function for rapid preprocessing, followed by visualization and data processing. This parallel preprocessing takes only a few seconds in comparison with several tens of minutes reported previously. As a result, clinicians instantly access recent data. We assessed 5,198 patients with prostatectomy data and PSA follow-up records.

Second, the flexible visualization function of the PCT-Map, which expands the axis of visualization when the current axis does not encompass new data including medication or treatment, includes not only the recent data but also previous clinical data. Because the entire visualization step is performed automatically and instantly, new patient data are automatically displayed if the format is correct.

The final advantage is the automatic medical factor calculation, which generates PSADT and BCR points from PSA kinetics. Because

this is time-consuming when performed manually, the automatic calculation function of the PCT-Map significantly reduces this duration. Clinicians access the calculated data on PSADT and BCR even among outpatients. PSADT and BCR are important factors influencing clinical decisions regarding the prognosis of prostate cancer after radical prostatectomy. Recurrence or a later incidence would be assumed by these factors. Because the PCT-Map is associated with the data from test results, it preprocesses laboratory findings, surgery, and treatment data and then determines the PSADT and BCR instantly for specific patients. Clinicians can assess its functionality to elucidate the feasibility of the PCT-Map, they can also assess these visualizations to obtain accurate information by accessing the PCT-Map, e.g., if clinicians use intuitive PSADT to make early decisions prior to disease progression, eventually, the patients will promptly receive appropriate treatment and present more favorable outcomes.

Furthermore, the PCT-Map facilitates the ultrasensitive PSA tracing to elucidate the micro-kinetics of PSA values temporally. Based on the ultra-sensitive PSA values, clinicians examine treatment outcomes for future events.<sup>26</sup>

In spite of many benefits of the PCT-Map, there are some limitations. Although the PCT-Map is optimized for prostate cancer with radical prostatectomy, it also can be used for radiation therapy with minor adjustments including specific BCR definitions for radiation therapy. Future studies are required to evaluate other diseases or other treatment strategies further, wherein it must be modified for certain diseases. However, the flexible function of the PCT-Map can yet be harnessed for other diseases for dynamic visualization. Because the PCT-Map has no information of patients transfer, serial data from some patients do not encompass entire observation periods. The PCT-Map would help determine the missing data on patients to determine the accuracy of the information regarding initial PSA to determine the BCR point. For updating patients' data, the PCT-Map needs new data from EMR system manually. To make autonomous data feeding, it needs to build pipeline from EMR system to the PCT-Map. However, it is out of this study's boundaries.

Because the PCT-Map uses standard R packages, any EMR system can implement it without changing their environment. The PCT-Map also has functionalities of web-server which is available to anybody who connects to the server. To install the PCT-Map, implementor will copy the source codes and install R packages followed by running the PCT-Map server.

The subsequent version of the PCT-Map will convey further information, including Gleason's score and staging to determine more factors. Using the labeling function of the PCT-Map, we intend to use machine learning or artificial intelligence approaches to predict probable patient outcomes.

We developed a practical CDSS called the "PCT-Map" for the clinicians, which would help them access complete serial data of patients without manual curation of EMR data. Furthermore, patient data were visualized in an intuitive manner. The values of the PCT-Map would help clinicians manually analyze the patient clinical data without actually using the PCT-Map. The PCT-Map projects accurate temporal data for prognosis management of radical prostatectomy.

#### Author contributions

Jihwan Park wrote the manuscript and contributed to the development of the PCT-Map. Mi Jung Rho helped write the manuscript and develop the PCT-Map. Hyong Woo Moon helped write the manuscript and test the PCT-Map. Yong Hyun Park helped write the manuscript and test the PCT-Map. Choung-Soo Kim, Seong Soo Jeon, and Minyong Kang helped collect and validate data.

Ji Youl Lee supervised the study and tested the PCT-Map. All four authors substantially contributed to this study through their areas of expertise.

#### Conflicts of interest

The authors declare no conflict of interest.

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