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Nomograms as Predictive Tools for Prostate Cancer Patients Who Had Radical Prostatectomy

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Abstract

Prostate cancer is the most common solid cancer for men in the developed countries. Radical prostatectomy is the most preferred treatment modality for localized prostate cancer. Individual decision making is necessary for each patient because of the diversities in the biological characteristics of the prostate cancer. The prediction of pathologic stage, prognosis and cancer specific mortality after curative therapy and quality of life issues are essential for counseling and tailoring treatment in possible candidates of radical prostatectomy. Several studies demonstrated that nomograms are the best predictive tools regarding the other prediction models. For better understanding the nomograms in radical prostatectomy patients, they should be classified according to categories for their use. PSA, Gleason grade and clinical stage are seemed to be the most important prognostic factors in patients who are candidates for radical prostatectomy. Additionally, the pathological parameters are remarkable prognostic criteria. The Partin tables for predicting the radical prostatectomy pathology and Kattan nomograms for predicting the biochemical recurrences free survival rates are the most frequently used nomograms. Today, these nomograms should not replace the clinical decisions but they give significant information for the patients' prognosis, treatment selection and follow up.

Keywords: Nomogram, Prediction, Prostate Cancer, Prognosis, Radical Prostatectomy

1. Introduction

Prostate cancer is the most common solid cancer for men in the developed countries [1]. Radical prostatectomy is the most preferred treatment modality for localized prostate cancer. Individual decision making is necessary for each patient because of the diversities of the biological characteristics of the prostate cancer. [2]. Selection of proper treatment for individual patient is crucial to improving the propensity of cure and survival. The prediction of pathologic stage, prognosis and cancer specific mortality after curative therapy and quality of life issues are essential for counseling and tailoring treatment in possible candidates of radical prostatectomy. Researchers have developed predictive and prognostic tools that are based on statistical models for making more accurate risk estimation. Contemporarily, these tools are nomograms, risk groupings, artificial neural networks (ANN), probability tables such as "Partin staging tables" and CART (classification and regression tree) analyses [3-8]. Several studies demonstrated that nomograms are the best predictive tools regarding the other prediction models [9,10].

2. What Is a Nomogram?

Statistically, a nomogram is defined as graphical calculating scale for related mathematical formula. In medical science, nomograms are the methods for predicting specific outcome (biochemical recurrences for prostate cancer, breast cancer mortality etc.) and prognosis by using the significantly prognostic parameters of the disease. For prostate cancer, it is aimed to make an assumption by using the prostate cancer data (prostate specific antigen (PSA), digital rectal examination (DRE), Gleason score, age, race, etc.) (3). Despite the fact that nomograms are developed for each stage of the prostate cancer, they have intensively been studied for localized prostate cancer in recent years. Commonly used nomograms are Partin nomogram (tables) for predicting the radical prostatectomy (RP) pathology and Kattan nomograms for predicting biochemical recurrences free survival [2].

The prediction accuracy of nomograms should absolutely be assessed and validated internally and externally. However, the application of such nomograms may be nonsense without understanding relationship between the parameters. To better understanding the nomograms in prostate cancer, they should be classified according to categories for their use (**Table 1**).

In this review, we discussed the prediction models associated with radical prostatectomy (RP).

2.1. Nomograms for Prediction of Pathological Parameters after Rp (Table 2)

Radical prostatectomy is frequently preferred treatment options for organ confined prostate cancer. In order to predict the pathology of the RP and the most suitable treatments for particular patients, several nomograms have been developed [2]. In these nomograms, the Preoperative parameters are used such as PSA, Gleason score, clinical stage, cancer volume in biopsy and PSA density.

2.1.1. The Predictions for Pathological Stage (Partin Look-up Tables and Others)

In 1987, Oesterling *et al.* developed a multiple logistic regression analysis to predict the pathological stage by using prostate acid phosphatase (PAP) , clinical stage and Gleason grade for 275 patients and it was the first publication in this topic [11]. Later, Narayan *et al.* set up the probability graphics by using the clinical stage, PSA, Gleason grade and transrectal ultrasonography [12]. Subsequently, the "Partin" look-up tables were developed to predict the pathological stage are the frequently used models.

The Partin tables are first formulated through the patients' data at Johns Hopkins University in 1993 [3]. The Partin Tables were updated in 1997, 2001 and 2007 [13-15]. The aim of the Partin Tables is to predict the pathological stage using 3 pre-operative parameters as clinical stage (TNM classification), Gleason grade and serum PSA. In clinical practice, it is performed in order to determine the probabilities for organ-confined diseases, seminal vesicular and lymph node involvement.

The prediction accuracy of any nomogram should be tested through validation (approval) processes, is conducted by the other data sets or populations. The Partin tables were validated by Blute *et al.* at Mayo Clinic in 2000 and by Greafen *et al.* on European patients in 2003. They stated that use of Partin tables is appropriate for both groups [16,17]. Also, Augustin *et al.* firstly compared the two Partin tables (1997 and 2001) and validated in 2004 [18]. The validation of 2007 Partin tables was accomplished by using SEER (Surveillance Epidemiology and End Results) database of American National Cancer Institute in early 2010. They found that the discrimination power of Partin tables for seminal vesical and lymph node involvement was high but is limited for predicting extracapsular extension and localized disease [19].

Owing to rising PSA screening over the years in the world, increased number of organ confined cancer was diagnosed due to early detection of prostate cancer in our

Table 1. Classification of nomograms for prediction of radical prostatectomy related outcomes.

1) Nomograms for predicting pathological parameters and stages after RP
- The predictions for pathological stage (Partin tables and others)
- Nomograms to predict the organ confined diseases and extracapsular involvement
- Nomograms for the prediction of SV invasion and lymph node involvement
- Nomograms to predict the surgical margin status
- Nomograms to predict the Gleason score upgrade
- Nomograms to predict the location of the tumor (peripheral zone and transitional zone) and tumor volume
- Nomograms to predict clinically insignificant cancers

2) Nomograms to predict PSA recurrence/disease free/general survival after RP
- Nomograms with the data prior to RP
- Nomograms with the data after RP

3) Nomograms to predict Prostate Cancer Specific Mortality After RP

4) Nomograms to predict the quality of life after RP

RP: Radical Prostatectomy; SV: Seminal Vesicle.

Table 2. Nomograms for predicting pathological parameters in radical prostatectomy.

Referrence	Predictions	Parameters	Number of patients	Accuracy (%)	Validation
Narayan *et al*. [12]	Pathologic stage	Biopsy based Stage, Biopsy Gleason sum, PSA	813	Non-specified	NA
Partin *et al*. [3]	Pathologic stage	Clinical stage, Biopsy Gleason sum, PSA	703	Non-specified	Externally and updated
Partin *et al*. [14]	Pathologic stage	Clinical stage, Biopsy Gleason sum, PSA	4133	72	Internally and Externally
Badalament *et al*. [20]	Organ-confined disease	Clinical stage, PSA, ratio of positive cores, percentage of positive cores	192	86	NA
Ohori *et al*. [21]	Side specific extracapsular extension	PSA, Clinical stage, Biopsy Gleason sum (side specific), percentage positive cores (side specific), percentage of cancer in cores (side specific)	763	81	Externally
Steuber *et al*. [22]	Side specific extracapsular extension	PSA, Clinical stage, Biopsy Gleason sum, percentage positive cores, percentage of cancer in positive cores	1118	84	Internally
Satake *et al*. [23]	Side specific Extracapsular extension	PSA, Clinical stage, biopsy Gleason sum,maximum precent of cancer on each side	354	79.9	Internally
Koh *et al*. [24]	Seminal vesical invasion	PSA, Clinical stage, primary ve secondary Gleason sum, percentage of cancer at base	763	88	Internally
Baccala *et al*. [25]	Seminal vesical invasion	Age, PSA, Biopsy Gleason sum, Clinical stage	6740	80	Internally
Gallina *et al*. [26]	Seminal vesical invasion	PSA, Clinical stage, Biopsy Gleason sum, percentage positive cores	896	79	Internally ve Externally
Ohori *et al*. [27]	Seminal vesical invasion	PSA, Clinical Stage, Biopsy Gleason score, presence of cancer at base	466	87	Internally
Cagiannos *et al*. [28]	Lymph node involvement (limited)	1) PSA, Clinical stage, Biopsy Gleason sum	5510	76	Internally
		2) PSA, Clinical stage, Biopsy Gleason sum, institution		78	Internally
Briganti *et al*. [29]	Lymph node involvement (extended)	1) PSA, Clinical stage, Biopsy Gleason sum	602	76	Internally
		2) PSA, Clinical stage, Biopsy Gleason sum, number of lymph node	781	79	Internally
		3) PSA, Clinical stage, Biopsy Gleason score, percentage positive cores	278	83	Internally
Choi *et al*. [30]	Pelvic lymph node involvement	Age, PSA, biopsy Gleason sum, positive cores ratio, maximum percent of tumor in any core	945	79.9	Internally
Chun *et al*. [31]	Gleason upgrade	PSA, Clinical stage, primary ve secondary Gleason sum	2982	80	Internally
Chun *et al*. [32]	Clinically significant Gleason upgrade	PSA, Clinical stage, Biopsy Gleason sum	4789	76	Internally
Stackhouse *et al*. [33]	Gleason upgrade	Age, biopsy Gleason sum, PSA, prostate weight, positive-to-total core ratio, maximum percent of cancer in cores	1701	72.4	Internally
Steuber *et al*. [34]	Tumor Location (TZ vs PZ)	PSA, Biopsy Gleason sum, positive core ratio at midprostate only, number of positive cores at base, cumulative percentage biopsy tumor volume	945	77	Internally

Peller *et al*. [35]	Tumor volume	Biopsy Gleason sum, number positive sextant cores and PSA	102	Non-specified	NA
Kattan *et al*. [36]	Clinically indolent cancer (tumor volume < 0.5 cm^3, organ confined and gleason grad e < 4)	1) PSA, primary ve secondary Gleason sum	409	64	Internally
		2) PSA, TRUS volume, primary ve secondary Gleason sum, percentage positive core		74	Internally
		3) PSA, Clinical stage, TRUS volume, primary ve secondary Gleason sum, milimeter of the positive core, milimeter of the negative core		79	Internally

country as same. Validation of the Partin nomograms has been conducted by Eskiçorapçı *et al*. with the participation of 1043 patients from 13 different centers in Turkish population [37]. In conclusion, the urologists should be keeping in mind that the Partin tables are only beneficial for predicting the pathological stage but not prognosis or biochemical recurrences.

2.1.2. Nomograms to Predict the Organ Confined Diseases and Extracapsular Involvement

Badalament *et al.* have developed a formula which calculates the probability for organ confined disease by using Gleason grade, nuclear grade, PSA and tumor involvement rates [20]. Later, the models which was calculating the probability of extracapsular involvement by using the Gleason grade, age, PSA and tumor involvement rates have been established and some of them were validated [38]. These models are not widely used because of complexity of the parameters (nuclear grade, total tumor involvement rate etc.). Partin tables may predict the extracapsular involvement but it fails to locate the effected side. Therefore, Ohori *et al*. and Steuber *et al*. developed the specific prediction nomograms for side specific extracapsular involvement [21,22].

2.1.3. Nomograms for the Prediction of SV Invasion and Lymph Node Involvement

The prediction of seminal vesicle and lymph node involvement is very important because these patients have generally worse prognosis and the success rate of radical surgery or radiotherapy is very low. Predictions for these patients have advantages in order to select the proper adjuvant treatment. Many researchers have been developed the models to predict the seminal vesicle and lymph node involvement [24-26]. However, these models could not take place in clinical practice due to diagnosing the diseases at earlier stages and founding more comprehensive prediction models like Partin tables. On the other hand, Ohori *et al.* recently developed a nomogram which predicts seminal involvement by using PSA, clinical stage, Gleason sum and cancer at the base. It was stated the accuracy of the nomogram was 87% [27]. The results of this nomogram are promising.

Eventually, Cagiannos *et al.* developed a prediction model for limited lymph node dissection and Briganti *et al.* developed for extended lymph node dissection. These nomograms may be helpful to make a decision for selecting the patients who need lymphadenectomy [28,29].

2.1.4. Nomograms to Predict the Surgical Margin Status

The positivity of surgical margin is an important prognostic parameter for the prediction of PSA relapse after RP. However, none of the nomograms predicting the surgical margin has been validated to date and they are not widely used [39,40].

2.1.5. Nomograms to Predict the Gleason Score Upgrade in RP

Gleason grade of RP is generally higher than the biopsy Gleason grade. D'Amico *et al.* developed a nomogram to predict the Gleason score upgrade and has recently been validated [7,31]. In addition, Chun *et al*. have developed a model to predict the high increases in Gleason grade with their nomograms and was internally validated [32]. Stackhouse *et al*. conducted a nomogram by using age, PSA, prostate volume, biopsy Gleason sum, ratio of positive biopsy core and maximum percentage of cancer in cores. The accuracy of nomogram was 72.4% [33]. Capitonio *et al.* developed their nomograms by using PSA, clinical stage, primary and secondary Gleason score in biopsy. The concordance index (c-index) was calculated as 74.89% [41]. These nomograms may be used especially for cryotheraphy, HIFU (high intensity focused ultrasonography) and active surveillance.

2.1.6. Nomograms to Predict the Location of the Tumor (Peripheral Zone and Transitional Zone) and Tumor Volume

The fact that organ confined disease rate of the transitional zone prostate cancer is higher despite the high PSA levels. Steuber *et al.* have developed a nomogram for predicting the transitional zone prostate cancer which c-index was 77% [34]. Peller *et al.* have developed another nomogram to predict the tumor volume in the prostate. However, this nomogram could not be widely used in view of including small number of patients and data of sextant biopsy [35].

2.1.7. Nomograms to Predict Clinically Insignificant Cancers

The most of prostate cancers are clinically insignificant. Besides the nomograms predicting the clinically insignificant prostate cancers, the three nomograms were developed by Kattan *et al.* is widely used. The nomograms are based on the criteria of Epstein *et al.* [36]. These nomograms may be useful for the elderly patients with high co-morbidity which require especially conservative approach.

2.2. Nomograms to Predict Biochemical Recurrence, Disease Free and General Survival after RP (Table 3)

2.2.1. Nomograms with the Data Prior to RP

After the Partin tables which were widely accepted for predicting the pathological stage, nomograms have been developed for prediction of survival which is the primary end point for prostate cancer. The most frequently used nomogram is the pre-operative Kattan nomogram, was firstly developed in 1998 [4]. The Kattan nomogram represents 5 years biochemical recurrence free survival rates by constituting PSA, clinical stage, Gleason grade. Kattan nomogram seems to have some advantages such as easy to apply, predicts progression free survival and defines the requirement of adjuvant treatments. The accuracy of the nomogram is increased by adding İn- terlökin-6 soluble receptor and transforming growth factor beta-1 [42]. In 2006, a new version of Kattan nomogram which predicts 10-years survival was published [43]. In our country, the validation of Kattan nomogram is recently accomplished by Eskicorapci *et al.* In this study the two pre-operative Kattan nomograms (developed in 1998 and 2006) validated and c-index was found as 68% and 70%, respectively [44].

The prediction model was developed by D'Amico *et al.* is similar to the Kattan nomogram [45]. This model predicts 10-years biochemical recurrences free survival with pre-operative PSA, Gleason grade and tumor stage. The patients are divided into three groups:

1) Low risk: Stage T1c - T2a, PSA ≤ 10 ng/mL and Gleason grade ≤ 6 (10 years progression free survival is 83%)

2) Medium risk: Phase T2b, PSA > 10 ng/mL ve < 20 ng/mL veya Gleason grade = 7 (10 years progression free survival is 46%)

3) High risk: Phase T2c, PSA ≥ 20 ng/mL veya Gleason grade ≥ 8) (10 years progression free survival is 29%)

Both nomograms (D'Amico and Kattan) predict the PSA progression but not mortality. The life survival of most patients is high despite PSA recurrence. These nomograms are useful to identify requirement of adjuvant treatment, predict disease free survival and select the patients for clinical trial.

2.2.2. Nomograms with the Data after RP

In 1999, Kattan *et al.* developed a nomogram to predict 5 years survival by comprising PSA, Gleason grade, capsular invasion, surgical margin status, seminal vesicle invasion and lymph node involvement. (56) These nomograms have been validated and widely used [46]. Stephenson *et al.* represents a new nomogram to predict 10 years progression free survival with additional parameters [47]. Moul *et al.* drew up tables predicting 3-5-7 year's survival without recurrence in 2001 [48]. This table is involved with PSA, race, Gleason score of RP and pathological stage. The other researchers namely Han *et al.*, Bauer *et al.*, Blute *et al*. and D'Amico *et al*. conducted similar models [49-52].

Recently, Morieira *et al.* designed a study to determine whether the Postoperative nomograms are affected by race with comparison of 7 nomograms. They stated all nomograms have similar performance regardless of their racial characteristics [53]. In addition, a study conducted to determine the effects of lowered PSA at diagnosis with rising PSA screening over the years leads to the clinical stage migration. They found it does not reduce Postoperative Kattan nomogram prediction accuracy [54]. Furthermore, the nomograms were developed for predicting early (2 years) and aggressive (9 - 12 months) recurrence after radical prostatectomy. Walz *et al*. set up a nomogram to predict early recurrence with 6 parameters and c-index was found as 82% [55]. Schroeck *et al.* developed a nomogram with 8 variables for predicting aggressive biochemical recurrence and compared with nine nomograms. They stated their nomogram is superior for determining aggressive recurrence [56]. Afterwards, they recalibrated and externally validated their nomogram [57].

2.2.3. Nomograms to Predict Prostate Cancer Specific Mortality after RP

Prostate cancer related mortality after RP is another important issue for prediction models. Stephenson *et al*. set up a nomogram to predict 15 years survival and c-index was found as 82% [58]. Indeed, Porter *et al*. developed a nomogram with constituting age, pathological stage, pathological Gleason sum, performing lymph node dissection and adjuvant radiotherapy data to determine 20-year disease-free survival after RP and c-index was 76.3% [59].

2.2.4. Nomograms to Predict the Quality of Life after RP

Although cancer specific survival has always been the

Table 3. Nomograms to predict biochemical recurrence, disease free and general survival after RP.

Referrences	Pre vs Postoperative	Variables	Number of Patients	Biochemical recurrneces (year)	Accuracy(%)	Validation
D'Amico *et al*. [51]	Preoperative	PSA, Clinical stage, biopsy Gleason sum, percentage positive cores	823	4	80	Internally and Externally
Kattan *et al*. [4]	Preoperative	PSA, Clinical stage, primary ve secondary biopsy Gleason grade	983	5	74	Internally and Externally
Stephenson *et al*. [43]	Preoperative	PSA, Clinical stage, biopsy Gleason sum, year of surgery, number of positive ve negative cores	1978 and 1545	10	76 and 79	Internally and Externally
Cooperberg *et al*. [60]	Preoperative	Age, DRE, number of previous negative biopsy, history of HGPIN ve ASAP, PSA, PSA velocity, family history, time to first biopsy, time to previous biopsy	1439	3 and 5	66	Internally and Externally
Graefen *et al*. [61]	Postoperative	Pathologic stage, volume Gleason grade 4/5,	2393	3,5	76	NA
McAleer *et al*. [62]	Postoperative	Gleason grade, stage, surgical margin, PSA	2417	7	Non-specified	Internally
Kattan *et al*. [5]	Postoperative	PSA, Gleason sum, extracapsular extension, seminal vesical invasion, lymph node invasion, surgical margin status	996	5	88	Internally and Externally
Stephenson *et al*. [47]	Postoperative	PSA, Gleason sum, extracapsular extension, seminal vesical invasion, lymph node invasion, surgical magrin status	1881, 1782 and 1357	10	78 - 86	Internally and Externally
Stephenson *et al*. [63]	Postoperative	Age, PSA, pathological Gleason score, pathological stage, year of surgery, surgical margin status	7160	7	85	Internally
Walz *et al*. [55]	Postoperative Early Recurrence (<2 years)	Age, PSA, pathological Gleason sum, surgical magrin, extracapsular extension, seminal vesical invasion and lymph node invasion	2911	Non-specifie d	82	Internally and Externally
Schroeck *et al*. [57]	Postoperative Agressive Recurrence (<9 months)	PSA, surgical margin status, seminal vesical invasion, extracapsular extention, Gleason score, prostate weight, African American, year of surgery	2599	5	83	Internally, Externally and Recalibrated

first end point, quality of life should also have an important place after curative treatments. The study which includes Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) data was produced to predict continence, erection status with physical and mental outcomes in the first year after RP [64]. This nomogram predicts characteristics of the preoperative tumors (clinical stage, PSA and Gleason grade) as well as the quality of life prior to surgery. Meanwhile, age and income status as well as co-morbidity were observed independent prognostic factors for prediction of the life quality. In addition, the good physical conditions without co-morbidity and healthy moods may induce rapid recovery to the pre-operative condition.

3. What Are the Limitations of Nomograms?

Most of the series constituted the nomograms with pre-operative parameters are developed by retrospective RP data. However, the prediction accuracy of nomograms may be affected by altering the population characteristics over the years. In PSA era, newly diagnosed prostate cancer patients have better stage and grade than before. Therefore, the nomograms should be updated and validated periodically. On the other hand, benefits from diagnosis and treatment of prostate cancer are not homogenous when considering the long clinical course and low mortality. Determining the weight of prognostic factors on prostate cancer outcomes should be defined

individually and in prediction model at the same time. For this purpose, Kattan nomograms and Albertsen tables are widely used [65,66].

To date, any model has perfect prediction performance. Additionally, some risk factors affecting the prognosis are not included in several nomograms. However, the models cannot achieve 100% accuracy even if all factors add into the nomograms. To increase the accuracy of nomograms, new biomarkers and imaging techniques have been investigated [42,67].

4. Conclusions

Predicting the clinical course of cancer is challenging for all patients. The urologists are willing to predict the pathological stages and possible scenarios after curative interventions. Therefore, the prognostic factors and nomograms are the frequently applied sources. PSA, Gleason grade and clinical stage are considered to be the most important prognostic factors. In addition, the pathological parameters are remarkable prognostic criteria. The Partin tables for predicting the radical prostatectomy pathology and Kattan nomograms for predicting the biochemical recurrences free survival rates are the most frequently used nomograms. Today, these nomograms should not replace the clinical decisions but they give significant information for the patients' prognosis, treatment selection and follow up.

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