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Nomograms as a Tool in Predicting Prostate Cancer Prognosis

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Abstract

Prostate cancer (PCa) is a heterogeneous disease with different disease states. Clinical judgment has significant biases. Nomograms are graphical calculating tools that use several clinical variables to determine a specific clinical outcome. Nomograms as prediction tools use multiple variables and continuous variables continuously, and their characteristics include patient populations, clinical end points, accuracy, and whether internal and/or external validations were performed. Numerous nomograms are available for most PCa stages, and their availability and accuracy make them powerful tools for the improvement of clinical prediction and important aids in personalised medicine for both patients and physicians.

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1. Introduction

Prostate cancer (PCa) is the most common malignancy in European and North American men. According to estimates in 2006, 345 900 (20.3%) new cases of PCa were diagnosed in Europe out of 1.7 million new cancer cases in males [1]. In the United States, 189 000 newly diagnosed PCa cases occurred in 2007 [2]. Since the use of serum prostate-specific antigen (PSA) as a useful marker for PCa screening, a dramatic change has occurred in the pattern of patients who are diagnosed with PCa. Despite the controversies regarding the survival benefit of PCa screening by PSA [3–4], its effect on downstaging at diagnosis is clear, and the association between PSA screening and PCa mortality has been established in recent studies [5]. Most patients are being diagnosed with clinically confined disease, and the rate of metastatic disease at presentation has dramatically decreased: 20% (1973–1979), 16% (1985–1989), and 5% (1995–2001).

PCa has unique features that complicate the decision-making process. The natural history of the disease is prolonged because of the relatively indolent biology and lead time of diagnosis. Different clinical variables exist, such as clinical stage, PSA level, and pathology parameters (Gleason score, number of involved cores, and percentage of involved tissue). Different treatments methods are available—surgery, radiation therapy (RT), minimally invasive procedures, and medical and active surveillance—and the efficacy of local therapy differs in correlation with the clinical variables.

2. Evidence acquisition

Clinical judgment is the basis for patient evaluation and for decision making in medicine; however, it is prone to several biases. Clinicians do not recall all cases equally, and the prediction of outcome is frequently chosen according to the desired one rather than to the one with the higher probability. The individual impact of the different clinical variables on outcome prediction varies, and the clinician's ability to evaluate each variable is limited. The decision-making process for an individual with localised PCa needs must consider additional information beyond the cancer data, including the patient's age, comorbidities, life

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Table 1 – Nomograms predicting biochemical recurrence following radical prostatectomy according to preoperative variables*

Patient population	End point	Author	Number	Accuracy	Validation
RP	BCR	Kattan et al, 1998 [6]	983	74 (internal)	Internal and external
RP	BCR	Stephenson et al, 2006 [11]	1978	76–79	Internal and external

RP = radical prostatectomy; BCR = biochemical recurrence.
*Adapted from Shariat et al [7].

Table 2 – Nomograms predicting biochemical recurrence following radical prostatectomy according to postoperative variables*

Patient population	End point	Author	Number	Accuracy	Validation
RP	BCR	Kattan et al, 1999 [12]	996	89 (internal)	Internal and external
RP	BCR	Stephenson et al, 2005 [13]	1881	78–86	Internal and external

RP = radical prostatectomy; BCR = biochemical recurrence.
*Adapted from Shariat et al [7].

Table 3 – Nomograms predicting biochemical recurrence following radiation therapy according to pretreatment variables*

Patient population	End point	Author	Number	Accuracy	Validation
External RT	BCR	Kattan et al, 2000 [14]	1042	73	Internal
Brachytherapy	BCR	Kattan et al, 2001 [15]	920	61	Internal and external

RT = radiation therapy; BCR = biochemical recurrence.
*Adapted from Shariat et al [7].

expectancy, and preferences regarding potential toxicity. Traditionally, the solution for the above-mentioned limitations was the creation of risk groups. A specific clinical variable was used to classify patients into these risk groups, and then additional variables were used for further classification. The patient could have high-grade cancer according to his prostate biopsy, and further classification would be based on his PSA and clinical stage. The use of such models is easy and rapid; however, their accuracy is not optimal. The reliance on a single variable also creates heterogeneous groups regarding therapy outcomes within a specific risk group.

Despite the data from randomised, controlled trials on large patient populations, the individual patient needs an answer for his personal situation. Do all patients with positive surgical margins benefit from adjuvant RT following radical prostatectomy (RP)? Should chemotherapy be used for all patients with hormone-refractory prostate cancer (HRPC)? It is clear that additional information is needed beyond the message from the available randomised, controlled trials that evaluated the specific clinical question.

An alternative clinical tool for improvement of clinical judgment and to aid in personalised medicine is the nomogram. Nomograms are graphical calculating tools, usually with two dimensions, that use several clinical variables to provide an answer to a specific question. Nomograms are usually based on regression analysis and achieve a better accuracy prediction compared to risk groups as a result of their ability to use multiple variables and continuous variables continuously. Another advantage is that nomograms are based on multiple variables according to their impact on the predictive model rather than screening by initial univariate analysis.

For PCa patients, an important change in the estimation of prognosis emerged a decade ago. Kattan and colleagues published an important paper evaluating the outcome following local therapy for PCa according to pretherapy clinical data [6]. Since then, many nomograms have been introduced for PCa that include different disease states. In order to consider the usefulness of a specific nomogram, several issues must be reviewed besides the clinical question to be answered, including the nomogram's accuracy, its correlation between the predicted and observed risk, and whether a similar prediction was reached using an external dataset different from the one used for the creation of the model. The accuracy of a nomogram is indicated by its concordance index, ranging from 0.5 to 1. The closer the index is to 1, the better its predictive value. Because the model is based on the specific data from which it is created, the performance of external validation (the use of a different dataset for the model testing) is important.

3. Evidence synthesis

Recently, an inventory of PCa predictive tools classified according to their end points was published. One hundred eleven different tools were published [7]. The advantage of such a review is the ability of the individual physician (or patient) to verify the available tools for the specific end point and to evaluate it according to the inherent characteristics. Examples of nomograms classified by their patient population and end point are provided in Tables 1–4 (adapted from Shariat et al [7]). An additional aspect of the nomogram's use beyond its performance is it availability and complexity. Some of the current models are available

Table 4 – Nomograms predicting metastasis progression or survival*

Patient population	End point	Author	Number	Accuracy	Validation
External RT	Metastasis progression	Kattan et al, 2003 [16]	1677	81	Internal and external
Rising PSA following RP or RT	Metastasis progression	Slovin et al, 2005 [17]	148	69	None
Rising PSA following RP	Metastasis progression	Dotan et al, 2005 [18]	248	93	Internal
Androgen-independent PCa	PCa-specific death	Svatek et al, 2006 [19]	129	81	Internal
Progressive metastasis after castration	OS	Smaletz et al, 2002 [20]	433	71	Internal and external
ADT following RP	PCa-specific death	Porter et al, 2007 [21]	66	66	Internal
Metastatic HRPC	OS	Halabi et al, 2003 [22]	1101	68	Internal and external

RT = radiation therapy; PSA = prostate-specific antigen; RP = radical prostatectomy; PCa = prostate cancer; OS = overall survival; ADT = androgen-deprivation therapy; HRPC = hormone-refractory prostate cancer.
*Adapted from Shariat et al [7].

for personal use, such as for personal computers or online. As a result of the incorporation into a digital format, the process of adding patient clinical data and getting the specific outcome is short, and is often completed within a few seconds. Because of their advantages, several nomograms (Kattan's preoperative nomogram [6] and Briganti's lymph node nomogram [9]) have been recommended by the recent PCa guidelines of the European Association of Urology as a useful tool for patient consultation [8].

Despite the above-mentioned advantages of nomograms as prognostic prediction tools, several disadvantages should be considered. A nomogram is based on the dataset from which it is built. Most of the data are retrospective and have a selection bias, that is, a selection of patients for a specific local therapy. Consequently, the selection can be associated with a specific outcome. An example of the influence of dataset characteristics on the performance of the prediction tool is the prediction of positive lymph nodes during RP. Different datasets showed that the number of positive lymph nodes at RP ranges between 1% and 11% [9]. However, the probability of positive lymph nodes depends not only on the tumour and patient characteristics, but also on the surgical template, the surgeon's performance, and the number of removed lymph nodes during surgery. Therefore, the prediction of the probability of positive lymph nodes according to a nomogram based on a limited lymph node dissection's template might lead to inaccurate prediction. The variables used for the creation of a model are those available at a specific time. Additional variables, such as new biomarkers or imaging modality results, might add predictive impact [10]. In addition, most nomograms are based on datasets from academic centres, either from Europe or from the United States. Their outcomes might differ from outcomes achieved in community hospitals and different geographic areas, because the nomograms do not take into consideration important variables such as the quality of the provided therapy.

4. Conclusions

Despite their limitations, nomograms created from large and high-quality datasets can be transformed into accurate predictions and improve the process of clinical decision making. Nomograms are useful tools for improving clinical prediction and personalised medicine for both patients and physicians.

Conflicts of interest

The authors have nothing to disclose.

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