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Review article

Nomograms are key decision-making tools in prostate cancer radiation therapy

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Abstract

Background: The use of nomograms for predicting clinical endpoints has been well documented. Nomograms provide an individualized prognosis and help clinicians determine the effectiveness of treatment for a given patient. Early identification of potential treatment failure or toxicity allows alternative approaches to be considered, reducing unnecessary treatment, morbidity, and cost. This review aims to evaluate clinical potential of nomogram use for the management of prostate cancer radiotherapy patients.

Methods: PubMed, Embase, and Scopus were searched for literature published between 2006 and 2016. The reported correlation between measured and nomogram-predicted probabilities of biochemical control, disease progression, survival and toxicity was reviewed, through an analysis of concordance indexes and areas under the curves.

Results: Sixteen studies were reviewed. Outcomes predicted by the nomogram were very close to outcomes measured (concordance index of 0.7 and above) in the majority. But a combination of under and overestimation of outcome was also reported. The predictive accuracy of nomograms was very variable, however, most nomograms had accuracy greater than chance, indicated by a concordance index higher than 0.5.

Conclusion: Nomograms can be used as prognostic guides to aid clinical decision-making for prostate cancer patients until further research addresses the limitations presented in this review. Strict definitions of end points should be added to future models and perhaps models could be enhanced with the incorporation of genomic variables or tumor specific parameters.

Keywords: Nomograms; Individualized prognosis; Prostate cancer; Decision-making tool

1. Introduction

Prostate cancer is the second most common cancer worldwide with an estimated 1.1 million men diagnosed in 2012 [1]. It is the fifth leading cause of death from cancer in men, representing 6.6% of the total male cancer mortality [1]. In Europe, the largest 5-year survival increase was reported for prostate cancer (73.4%, 1999–2001 vs. 81.7%, 2005–2007) [2]. This survival increase reinforces the importance of accurate predictions of tumor control and functional outcomes for this group of patients, as more patients are surviving and dealing with the outcome and effects of treatment. Biochemical control, disease progression, survival, and toxicity are important influences on treatment decision analysis, and accurate predictions of these outcomes are paramount to patient management. In particular, access to these predictions early, uniquely allows clinicians to assess the potential need for a change of treatment strategy and ultimately enables more efficient patient management.

A nomogram is a predication tool based on statistical data obtained from a population with the same characteristic disease. Each variable included in the nomogram is assigned a value that represents its prognostic significance. A total point axis is obtained at the end of the nomogram which estimates a specific outcome. An unbiased prediction is obtained, accounting for the different clinical characteristics of the patient. The European Association of Urology recommends integration of recently developed and validated nomograms into the counseling process [3]. In a survey of radiation oncologists and urologists, 55% reported

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using prostate cancer nomograms [4]. Totally, 60% of clinicians were familiar/very familiar with the nomogram format vs. 56% for the look-up table and 21% for the decision tree [5]. In all, 74% rated the nomogram format as good/excellent vs. 69% for the look-up table and 17% for the decision tree [5]. Nomograms have the highest accuracy and superior discriminating characteristics for predicting outcomes in comparison to other prediction tools [6–8]. The increase in predictive accuracy is clinically significant from a health economic, medical and personal perspective [9] as nomograms focus on more personalized medicine with tailored risk predictions that allow efficient use of all available clinical data. Although there is evidence that nomograms are superior to other prediction tools, few studies directly compare the quality of nomograms predicting the same end-points.

Several nomogram limitations have been previously reported, including the retrospective statistical methodologic approach and the uncertainty regarding nomogram updating [9]. Nomograms that are not updated may not reflect the current gold standard of diagnosis and treatment. Additionally, there is a lack of understanding regarding the statistical foundations of nomogram construction, their precise interpretation, and evidence supporting their use [10].

External beam radiation therapy (EBRT) and brachytherapy are 2 well established forms of treatment for prostate cancer patients—approximately 60% of patients will receive RT [11]. Keyes et al. [12] estimated that more than 12,000 patients have been implanted for brachytherapy so far in all Canadian centers. Biochemical control, disease progression, survival, and toxicity are key end points to consider as they effect the patient's quality of life [13]. Toxicity following treatment includes gastrointestinal (GI) rectal bleeding, increased stool frequency, discomfort, rectal incontinence, proctitis, genitourinary (GU) obstruction, increased urinary frequency, nocturia, urinary incontinence, and dysuria [14]. Analysis of patient-reported outcomes among 1,643 men in the Prostate Testing for Cancer and Treatment (ProtecT) trial identified a peak in the severity of these symptoms at 6-month posttreatment [15].

Chun et al. [16] suggested that careful selection and knowledge of the nomogram in use is vital and extremely important in clinical practice. There is evidence that nomograms are superior to other prediction tools; however, few studies directly compare the quality of nomograms predicting the same end-points. This review aims to identify whether nomograms can accurately predict tumor control and functional outcomes for prostate cancer patients following EBRT including brachytherapy.

2. Methods

2.1. Data sources

Pubmed, Embase, and Scopus were searched to identify relevant studies. The following search terms were used; Prostate cancer AND nomograms AND (RT/brachytherapy/toxicity/biochemical control/survival/progression). Searches were also performed using different terms for prostate cancer including, "prostate neoplasm," "prostatic carcinoma," "prostate tumor," "prostate adenoma," and "prostate malignancy." Title/abstract screening was performed on the search results and articles were reviewed for inclusion. Studies were excluded if the nomogram was presented but no correlation was made between the actual and predicted outcome(s) for the participants. RT treatment methods included low-dose rate or high dose rate brachytherapy, 3-dimensional conformal RT and intensity modulated RT.

The reference lists of relevant studies were searched to further identify possible studies beyond the scope of the primary search. The last search was performed on July 1, 2017 (Fig. 1)

2.2. Type of studies

Retrospective cohort and case control studies, written in English, comparing predicted and observed outcomes of biochemical control, disease progression, survival, or toxicity were included.

2.3. Type of participants

Participants comprised of histologically proven prostate cancer patients, of any risk group, who were treated with RT including brachytherapy.

2.4. Type of interventions

Participants treated with either EBRT or brachytherapy were eligible. Numerical and graphical comparisons between actual and predicted outcomes (biochemical control, disease progression, survival, and toxicity) were included.

2.5. Outcome measures

Biochemical control can be analyzed for prostate specific antigen (PSA) failure/relapse and biochemical freedom from failure (BFFF). Biochemical relapse definitions differed and included the Houston and Phoenix definition (absolute nadir plus 2 ng/ml dated at the call), 2 consecutive PSA values $\geq$ 0.2 ng/ml and the Kattan modification of the ASTRO definition (3 PSA increases [with or without stable intervening PSA levels] and no PSA decreases). Disease progression incorporated the risk of clinical relapse or metastasis.

For survival, prostate cancer-specific survival (PCSS), biochemical failure free survival (BFFS), distant metastasis free survival, and life expectancy (LE) were analyzed.

Toxicity of the GU and GI system was analyzed. Slightly modified RTOG/EORTC acute toxicity scoring system to grade lower GI morbidity was used. Acute toxicity was also scored using a self-administered questionnaire based on the late effects of normal tissues—subjective, objective, management, and analytic (LENT-SOMA) scale.