Appropriate Use of Nomograms to Guide Prostate Cancer Treatment Selection

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Key Words

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Abstract

For decades physicians have attempted to accurately predict post-treatment outcomes before performing prostate cancer interventions. Use of basic clinical factors, such as clinical T-stage, biopsy Gleason sum, and pretreatment prostate specific antigen, has allowed some level of prediction of pathologic and clinical outcomes. However, these basic tables and risk stratification schema provide a broad range of potential outcomes. The rapid growth of retrospective research in prostate cancer has yielded an abundance of additional potential prognostic factors that may influence outcomes of interest; however, incorporating and understanding the significance of these ever-expanding factors is difficult for even the most experienced physicians. Nomograms incorporate these factors (including treatment-specific) and assign them relative weights to provide a probability of the outcome of interest on a graphical scale. They distill large numbers of data into a manageable format and provide the probability of outcomes on a continuous scale rather than in categoric groups. However, because they require a computation to generate a probability, they are not amenable to memorization, which decreases ease of use. Furthermore, these numbers still have associated confidence intervals and the models are largely derived from retrospective data, which have inherent drawbacks. Clinicians and patients should still exercise due diligence when interpreting the results of these nomograms, and these prediction tools should not serve as a stand-alone substitute for clinical decision-making. (*JNCCN* 2010;8:201–209)

For decades physicians have attempted to accurately predict post-treatment outcomes before performing prostate cancer interventions. Use of basic clinical factors, such as clinical T-stage, biopsy Gleason sum, and pretreatment prostate-specific antigen (PSA), has allowed some level of prediction of pathologic (e.g., pathologic T-stage and Gleason sum, nodal involvement) and clinical outcomes (e.g., biochemical failure, clinical failure). Although easy to use, these basic tables and risk stratification schema provide a broad range of potential outcomes. This may not be surprising given that the number of factors used in these predictive models is relatively limited. The rapid growth of retrospective research in prostate cancer has yielded an abundance of additional potential prognostic factors that may influence outcomes of interest; however, incorporating and understanding the significance of these ever-expanding factors is difficult for even the most experienced physicians.

Nomograms incorporate these factors (including treatment-specific) and assign them relative weights to provide a probability of the outcome of interest on a graphical scale. They have the advantage of distilling large numbers of data into a manageable format and provide the probability of outcomes on a continuous scale rather than in categoric groups. Because they require a computation to generate a probability, they are not amenable to memorization, which decreases their ease of use. However, the ubiquitous availability of portable computing and Internet access is making this less of an issue.

Clinicians and patients should still exercise due diligence when interpreting the results of these nomograms. Although the generation of a specific percent chance of an outcome is seductive, these numbers still have associated confidence intervals and the models are largely derived from retrospective data, which have inherent

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drawbacks. These prediction tools are useful in assisting physicians and patients but should not serve as a stand-alone substitute for clinical decision-making.

Background

Selecting the optimal treatment for localized prostate cancer is a daunting task for both patients and physicians. Unfortunately, few randomized data compare clinical outcomes for the primary local therapy options: radical prostatectomy (RP), external beam radiation therapy (RT), and brachytherapy. In the absence of prospective clinical trials, patients and physicians must rely on retrospective data and their resulting predictive models (e.g., risk stratification, look-up tables, nomograms) to make decisions.

Clinicians ultimately try to predict relevant outcomes for their patients based on the available presenting clinical factors. One schema would have the following chain of outcomes:

Clinical factors (T-stage, biopsy Gleason score, pretreatment PSA) → Pathologic end points (prostatectomy T-stage and Gleason score, margin status, nodal involvement) → Post-treatment end points (time to PSA failure, PSA kinetics) → Clinical outcomes (local failure, distant failure, cause-specific death, overall survival)

Understanding all the prognostic factors to determine these outcomes is challenging for any physician, and the use of predictive tools, such as nomograms, help focus attention on the most relevant factors and ease their clinical interpretation.

Before Nomograms

The precursors to current nomograms included lookup tables such as the Partin Tables.¹ These tables provided a reasonable prediction of pathologic outcomes (pathologic T-stage, nodal involvement) using available clinical factors (clinical T-stage, biopsy Gleason sum, pretreatment PSA). These pathologic end points could be correlated with clinical end points based on prior data. They also provided some guidance in the selection of therapy or the extent of pretreatment staging.

Subsequent stratification models sought to categorize men into different “risks” for recurrence (usu-

ally PSA failure) based on similar presenting clinical factors.^{2,3} In one risk stratification system developed by D’Amico et al.,³ patients were considered at low- (T1c–2a, Gleason ≤ 6, and PSA ≤ 10 ng/mL), intermediate- (T2b, Gleason 7, or PSA 10.1–20), or high- (T2c, Gleason 8–10, or PSA > 20) risk for experiencing biochemical recurrence after conventional local therapy defined as RP, external beam RT to a dose of 70 Gy, or brachytherapy. Estimated 5-year probabilities of PSA failure-free survival for these groups were greater than 85%, 85% to 50%, and less than 50%, respectively. Other groups used a similar grouping of favorable (T1c–2, Gleason ≤ 6, and PSA ≤ 10 ng/mL), intermediate (elevation in 1 factor regardless of magnitude), and unfavorable (elevation in ≥ 2 factors) to predict recurrence risks after radiation therapy.^{4,5} Current NCCN guidelines use a risk grouping of low (T1–2a, Gleason score ≤ 6, PSA < 10), intermediate (T2b–c, Gleason 7, or PSA 10–20), high (T3a, Gleason 8–10, or PSA > 20), and locally advanced very high (T3b–4).

These risk groupings have performed reasonably well in stratifying patients after local monotherapy and provide a basis for selecting the appropriate level of therapy for a given disease state. They are easy to memorize and use in clinical settings. Despite the relative simplicity of risk grouping stratification, they provide a foundation for selecting a reasonably appropriate level of therapy and subsequently stratifying outcomes for groups of patients rather than serving as a standalone prediction tool. Traditional risk stratification predicts a range of outcomes per risk group, which is most evident in the intermediate-risk group (e.g., 5-year biochemical control of 15%–85%).⁶ Subsequent modifications to this risk grouping have included distinguishing between Gleason score 4+3 and 3+4, percent positive biopsies, findings on endorectal coil MRI, and tertiary Gleason grade 5 component.^{7–12} In general, the more factors put into a prediction model, the more accurate the outcomes. Prediction models differ slightly from typical statistical models that test for associations between factors, for which a more parsimonious model may be preferred.

What is a Nomogram?

Not all predictive tools are actually nomograms. The term refers to a graphical device used to calcu-

late the approximate computation of a function or formula. Specific factors are assigned varying points based on their relative contribution to the outcome of interest. The sum of these points is then graphically associated with a corresponding probability of the outcome on a continuous scale. Similar to other predictive models, they use prior data to model (usually through a series of regression analyses or recursive partitioning analyses) an association between a combination of factors and the outcome of interest. Because most nomograms model outcomes on continuous rather than categorical scales, they have the potential to be more accurate than other models, such as risk group stratification.

The performance of a nomogram for predicting outcomes may depend on several factors independent of the statistical model. Evaluation of a nomogram for clinical use should consider the following elements:

1. Does the nomogram measure the outcome of interest?
2. What was the quality of the data used to derive the model? Because nomograms are typically developed from retrospective data (with their inherent selection and reporting biases), the quality of the native data must be understood (e.g., was a central pathology review performed, was treatment uniform and applicable to one's practice, was follow-up adequate).
3. How many factors does the nomogram require and are these readily available in the clinic? Increasing the number of factors (even if they do not meet the criterion of statistical significance) can increase the predictive accuracy of a model, and nomograms can integrate additional factors easily (especially in electronic format); however, reliance on an esoteric factor diminishes practicality.
4. Was the nomogram validated using an external data set? Ideally, nomograms should perform well on other foreign data sets.
5. Does the nomogram accurately predict outcome? This is usually represented as the concordance index (c-index), which in some studies is derived from a receiver–operator curve area, and in others a probability model of the outcome. In general, a perfect test will have a c-index of 1.0, whereas 0.5 is similar to flipping a coin. A reasonable threshold for a good test is greater than 0.7.
6. Was the nomogram calibrated? The overall accuracy of a nomogram does not guarantee the same level of accuracy for each subset of patients. For example, one popular nomogram had poorer performance in predicting outcomes when applied to a community-based cohort (CaPSURE) and overestimated success particularly in patients at lower risk for failure (< 35% risk for failure).¹³
7. Does the nomogram have the correct level of generalizability versus specificity? Most current nomograms are derived from data sets at larger tertiary care centers that may have varying expertise levels in therapy, pathologic analysis, and radiographic staging compared with other practices. Ideally, the nomogram should include data from multiple sources to maximize generalizability. However, if one's practice patterns are more consistent with a specific institution, then using a nomogram from that center may provide better accuracy.
8. Does the nomogram perform significantly better than simpler models? A nomogram should be tested against currently available prediction models to determine clinical superiority. One must also decide whether the improvement in predictive accuracy is substantial enough to warrant the effort.

Prediction of Pathologic Outcomes After RP

Numerous tools have been developed to predict pathologic features found at RP, which have provided the basis for subsequent nomograms. The initial and most widely used of these prediction tools are the Partin tables, which use preoperative clinical factors (biopsy Gleason score, clinical stage, and PSA level) to predict pathologic stage. The Partin tables were validated in 1997 and last updated in 2007.^{1–14} Although widely used in pretreatment planning, they have limitations. Because they do not include biopsy core involvement information that provides indirect measures of overall and side-specific tumor volume, they cannot predict side-specific tumor features, such as extracapsular extension. This information may alter the nerve-sparing strategy at RP. They also cannot predict which patients may have clinically insignificant or indolent cancers. Numerous additional nomograms were subsequently developed

that predict specific pathologic features and estimate clinically indolent disease.

A proportion of patients harbor clinically insignificant disease at diagnosis. Accurately identifying these patients using nomograms could distinguish candidates for active surveillance rather than definitive therapy. Based on the definition of clinically insignificant disease proposed by Epstein et al.¹⁵ (i.e., organ-confined cancer, ≤ 0.5 mL, and without Gleason pattern 4 or 5), Kattan et al.¹⁶ developed 3 nomograms to predict the probability of indolent cancer. These nomograms were found to be 64% to 79% accurate on internal validation, depending on the predictive factors included in the nomogram. In the most accurate of these nomograms (79% accurate), PSA, clinical stage, primary and secondary Gleason scores, transrectal ultrasound volume, length (mm) of cancer, and noncancer predictors were all included. These nomograms also were externally validated in a screening cohort.¹⁷

Patients with a likelihood of Gleason score upgrading from biopsy to final pathology may not be the best candidates for active surveillance. Preoperative knowledge of the probability of finding high-grade disease in the prostate specimen may also alter surgical technique or the decision to perform lymph node dissection. Chun et al.^{18,19} developed 2 nomograms, one predicting Gleason upgrading and the other predicting significant upgrading defined as a Gleason score increase either from 6 or less to 7 or greater or from 7 to 8 or greater between the biopsy and final pathology specimen. These nomograms were internally validated in large cohorts achieving high predictive accuracies of 76% and 80%, respectively.

Several nomograms have been developed to predict extracapsular extension of cancer. This finding is particularly important in candidates for neurovascular bundle preservation. Although preserving the neurovascular bundles may confer quality-of-life benefits, nerve-sparing techniques may result in positive margins in the presence of extracapsular extension. Because extracapsular extension is often unilateral, side-specific predictions could allow selection of patients for unilateral or bilateral nerve-sparing procedures.

In 2001, Graefen et al.²⁰ proposed an algorithm capable of predicting extracapsular extension in a side-specific manner that yielded 70% accuracy on external validation. Two additional nomograms as-

sessing side-specific extracapsular extension were developed; one in an American population of 763 patients and another in a larger population (N = 1118) of European men.^{21,22} A greater proportion of men included in the European cohort underwent extended prostate biopsy, which may explain its slightly higher accuracy compared with the American cohort (84% and 81%, respectively). However, because American and European patients may have different tumor characteristics at presentation, perhaps because of differences in screening practices, the generalizability of these nomograms is uncertain. Although the Partin tables are commonly used to predict extracapsular extension, these nomograms are more accurate and offer important side-specific information lacking in the Partin tables.

Because they are often associated with micro-metastatic disease, seminal vesicle and lymph node invasion are pathologic factors associated with high risks for recurrence after local therapy. Patients at high risk for these tumor characteristics may require multimodality therapy. Moreover, patients at high risk for lymph node involvement may benefit from extended lymph node dissection at RP. In a cohort of 763 patients, Koh et al.²³ developed a nomogram to predict seminal vesicle invasion with 88% accuracy through including a measure of the percent of cancer at the prostate base in addition to standard predictors.

Based on limited pelvic lymph node dissection in a cohort of 5510 patients, Cagiannos et al.²⁴ provided a nomogram predicting lymph node invasion. This nomogram yielded 76% accuracy compared with 74% for the Partin tables when tested in the same cohort. Compared with limited node dissection, extended pelvic lymph node dissection may better detect lymph node involvement, increasing the overall incidence of lymph node positive cancer. A nomogram predicting lymph node involvement in patients undergoing extended lymph node dissection was developed in a cohort of 602 patients with 76% accuracy on internal validation.²⁵ The same group developed an additional nomogram to help identify patients at low risk for lymph node involvement outside the obturator fossa (80% accuracy).²⁶ Nomograms can identify patients at low risk for lymph node invasion who might not need a node dissection, and conversely identify higher-risk patients who may benefit from extended dissection beyond the obturator fossa.

Predicting Biochemical Recurrence After RP

Prediction of biochemical recurrence after RP can be based on preoperative factors alone (before prostatectomy) or postoperative pathologic findings (after prostatectomy). Like the Partin tables for pathologic outcomes after RP, the Kattan nomograms represent the most widely known and used nomograms to predict biochemical recurrence after surgical treatment. In 1998, Kattan et al.²⁷ published the first preoperative nomogram predicting 5-year biochemical recurrence rates that was 74% accurate on internal validation and approximately 75% accurate on external validation. This was followed in 1999 by the publication of a postoperative nomogram also predicting 5-year biochemical outcomes.²⁸ In addition to preoperative PSA, the postoperative nomogram includes extracapsular extension, pathologic Gleason score, surgical margin status, seminal vesicle invasion, and lymph node involvement. External validation of this nomogram in an international cohort and in African-American men yielded accuracies of 80% and 83%, respectively.^{29,30} Although these nomograms are valuable, the 5-year end point will probably be inadequate in predicting the ultimate cure because many men will experience recurrence beyond 5 years of treatment.

Stephenson et al.^{31,32} updated the postoperative and preoperative Kattan nomograms in 2005 and 2006, respectively. The new preoperative nomogram predicted 10-year biochemical recurrence outcomes, adjusted for the year of surgery, and included biopsy information such as the number of positive and negative cores. An additional feature of this nomogram was its ability to estimate probability of recurrence at any point from 1 to 10 years after RP. The postoperative nomogram also extended the prediction interval to 10 years and included more contemporarily treated patients. This nomogram was developed in 1881 men and was externally validated in 2 cohorts with accuracies of 78% and 81%.

An initial critique of the Kattan nomograms was that, because they were developed in a patient population that mostly consisted of white men, they may not apply to African-American men. However, this was disproved when Bianco et al.³³ tested both nomograms in an African-American patient population and found that concordance indices for both nomograms were comparable to that in a cohort of

white men. Recently, a nomogram was developed to predict the 20-year risk for biochemical recurrence after RP.³⁴ This model's accuracy (77%–83%) was confirmed in 2 external validation cohorts.

Several recent studies suggest that surgeon experience may be predictive of biochemical outcomes after prostatectomy, even after controlling for individual patient characteristics.^{35–37} These data suggest that the number of cases a surgeon has performed should be included in recurrence nomograms and discussed with patients before surgery is considered. In a recent study, Kattan et al.³⁷ presented preoperative and postoperative nomograms incorporating surgeon experience. Data from 4 institutions (7724 patients) and 72 surgeons was collected. Surgeon experience was coded as the number of RPs performed by the surgeon before the patient's operation. Although surgeon experience at these institutions was shown previously to impact biochemical outcomes, and in some cases had a clinically significant impact on biochemical recurrence, incorporation of surgeon experience in these nomograms did not greatly affect the predicted probabilities.

Prediction of Metastasis in Patients With Biochemical Recurrence After RP

Although PSA recurrence is a valuable early end point predicted by most preoperative and postoperative nomograms, development of local or distant metastasis represent more important end points. Metastatic disease after RP is almost always preceded by a biochemical recurrence. In 239 men with a rising PSA after RP, Dotan et al.³⁸ developed a nomogram predicting the probability of a positive bone scan. PSA kinetic measures were an important component of this nomogram that were found to be 93% accurate on internal validation. Slovin et al.³⁹ developed a similar nomogram in 148 men with biochemical recurrence after initial treatment with either surgery or radiotherapy. Patients in this cohort had PSA doubling times of less than 12 months, and outcome was the length of predicted distant metastasis-free survival. Like the Dotan study, PSA kinetic measures were an important prognostic factor. The predictive accuracy of this model was 69% but not externally validated. The optimal timing of salvage hormonal therapy in patients with biochemical recurrence remains uncertain. These nomograms might help

identify patients who are candidates for earlier institution of hormonal therapy based on a higher risk for developing metastatic disease.

Predicting Response to Salvage Radiotherapy After RP

Approximately 30% of men treated with RP for clinically localized prostate cancer will experience biochemical recurrence within 10 years of surgery. Many of these patients will be candidates for salvage radiotherapy. Although most men will experience an initial fall in PSA level in response to this treatment, long-term disease control is less common, seen in 40% or fewer of treated patients. Stephenson et al.⁴⁰ developed a nomogram to predict the probability of cancer control at 6 years after salvage radiotherapy as measured by PSA progression-free survival. Using a multivariate Cox regression analysis, the model was constructed using a multi-institutional cohort of 1540 patients. Significant variables included in the model were PSA level before salvage radiotherapy, PSA doubling time, prostatectomy Gleason score, surgical margin status, androgen-deprivation therapy before or during treatment, and lymph node metastasis. The resultant nomogram was internally validated and had a c-index of 0.69. The potential morbidity of salvage radiotherapy argues against its indiscriminate use in patients who develop a detectable PSA after prostatectomy. This is the only nomogram that predicts outcome after salvage radiotherapy, and may be useful in selecting patients who are likely to have a long-term response to this treatment.

RT Nomograms

Traditional risk group stratification has used various clinical factors to predict outcomes (typically biochemical failure) after standard external beam radiation therapy (total doses approximately 70 Gy) and/or brachytherapy. This provided a foundation for including other factors (e.g., percent positive biopsies, MRI T-stage) to enhance their predictive ability. However, these risk groupings typically have not included detail regarding the actual treatment parameters (e.g., total radiation dose, use of hormone therapy), whereas nomograms have.

One popular nomogram by Kattan et al.⁴¹ used not only the clinical factors but also treatment fac-

tors such as total radiation dose in a continuous fashion. This nomogram was based on a single institution's large data set (N = 1042) using various external beam techniques and covered a relatively wide treatment era. It was validated using another historical data set from a separate institution. Its accuracy in predicting PSA failure was almost 75% and it performed better than traditional risk-grouping in predicting PSA outcomes.

However, some key aspects should be considered before using this tool. Both data sets were from an older era (mid-late 1980s to 1998), and radiation techniques and patient factors have since changed. Not all the radiation dose ranges were delivered using the same technique. The lower doses were delivered using older techniques, and the patients treated from that era may have different levels of presentation than patients treated in the more recent era of PSA screen-detected cancers. These latter patients likely were treated using modern techniques with higher radiation doses and also subject to stage and Gleason grading migration. The men with T2c tumors also had worse outcomes than those with T3a or T3b disease, which is counterintuitive and may be the result of physical examination variability, relatively few subjects in this group, or biased patient selection for treatment.

Furthermore, hormone therapy had little impact on outcomes in this data set and was not statistically significant in this model. This may have been because of the relatively short duration of hormone therapy (i.e., 3 months) and that the selection of patients for hormone therapy was based on gland volume rather than cancer-specific factors, which may have diluted its effect. Randomized studies have shown a disease-control benefit to slightly longer hormone treatments (i.e., ≥ 6 months).⁴²⁻⁴⁴ A subsequent update of the primary data set used for this nomogram has shown a statistically significant benefit associated with even 3 months of hormone therapy for higher-risk patients.⁴⁵

This nomogram was updated using a larger data set (n = 2253) in 2007, and now provides estimates of progression-free survival at 5- and 10-year intervals for 3-dimensional conformal RT and newer intensity-modulated RT.⁴⁶ The c-index of 0.72 was similar to the prior model; however, the impact of hormone therapy was more profound in the current model. In fact, the more recent nomogram suggested that the

impact of short-term neoadjuvant hormone therapy (typical duration 3 months) may be as beneficial as escalating the radiation dose from 70 to 84 Gy. Furthermore, the calibration of the nomogram suggests that it does not perform optimally in patients at intermediate risk for failure (i.e., progression-free probabilities 75%–65%). These differences may be caused by several factors, including changes in the patient population, longer follow-up, stage or Gleason score migration, or difference in the biochemical failure definition (nadir + a rise of 2 ng/mL).

A nomogram was also developed to predict biochemical outcomes after prostate brachytherapy with or without supplemental external beam RT.⁴⁷ A large data set ($n = 920$) from one institution was used to design the nomogram, and the 2 other large data sets ($n = 1827$ and $n = 765$, respectively) were used for validation. However, this prediction tool did not perform well with corresponding concordance indices of 0.61 and 0.64, respectively. A subsequent application of this nomogram to another single institution's experience showed that the predicted outcome was worse than that actually observed and was no better than chance in predicting biochemical failure.⁴⁸ This may have been caused by a multitude of factors, including variations in pathologic analysis, implant technique, and patient selection. A subsequent nomogram developed by Potters et al.⁴⁶ using a larger data set and more specific treatment-related factors (e.g., post-implant dosimetry and isotope type) is currently in press and has better performance (Potter, unpublished material).

The relative clinical significance of PSA failure as an end point is debatable. Kattan et al.⁵⁰ developed a nomogram to predict the probability of distant metastasis after external beam RT. Again this nomogram was developed using a large single-institution data set ($N = 1677$) and validated using a second institution's data set ($N = 1626$). The nomogram performed well with a c-index of 0.81. However, several limitations were cited that may attenuate the usefulness of this tool for clinical use. Many patients may have benefited from combined modality therapy with androgen suppression but were largely excluded from analysis. Furthermore, the use of salvage hormone therapy and repeat imaging were not regimented and subject to bias, which may have affected the event rate.

Conclusions

Nomograms represent important tools to provide insight and aid in the interpretation of many factors in a more manageable fashion for prognostic prediction. They not only help guide therapy decisions but also may also be used to determine the extent of pretreatment diagnostic staging and the intensity of posttreatment follow-up in higher-risk patients. In the absence of randomized comparisons between local therapies, nomograms may provide the additional insight to make a better informed decision. Despite their clinical usefulness, they are derived from retrospective data with all their inherent biases, and regardless of the perceived accuracy should not be considered a substitute for randomized trials. Although multivariable analysis can help control for known factors associated with outcome, randomization accounts for known and unknown confounding factors. One must consider that specific subtle reasons may have led patients or physicians to choose a certain therapy over another and these factors are difficult to consider (or even know) when seeing a new patient.

Although nomograms yield probabilities of outcomes on a continuous scale, the treating physician and patient still must determine the clinical significance of this number. Is a 50% versus 60% probability of failure clinically meaningful? (Both numbers seem dismal.) Furthermore, the resulting probabilities from nomograms have associated confidence intervals, which can be $\pm 10\%$ to 15% . Ideally, any prediction model should be tested in individual clinical practices to determine the validity for clinical use. Probabilities may help with decision-making, but for the patient the ultimate goal of being cured is still a binary outcome.

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