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Postoperative systems models more accurately predict risk of significant disease progression than standard risk groups and a 10-year postoperative nomogram: potential impact on the receipt of adjuvant therapy after surgery

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Abstract

- To compare the performance of a systems-based risk assessment tool with standard defined risk groups and the 10-year postoperative nomogram for predicting disease progression, including biochemical relapse and clinical (systemic) failure.
- Clinical variables, biometric profiles and outcome results from a training cohort comprising 373 patients in a published postoperative systems-based prognostic model were obtained.
- Patients were stratified according to D'Amico standard risk groups, Kattan 10-year postoperative nomogram and prognostic scores from the postoperative tissue model.
- The association of pathological variables and calculated risk groups with biochemical recurrence and clinical (systemic) failure was assessed using the concordance index (C-index) and hazard ratio (HR).
- Systems-based post-prostatectomy models to predict significant disease progression (post-treatment clinical failure) were more accurate than the D'Amico defined risk groups and the Kattan 10-year postoperative nomogram (systems model: C-index, 0.84; HR, 17.46; $P < 0.001$ vs D'Amico: C-index, 0.73; HR, 11; $P = 0.001$; 10-year nomogram: C-index, 0.79; HR, 5.06; $P < 0.001$).
- The systems models were also more accurate than standard risk groups for predicting prostate-specific antigen recurrence (systems model: C-index, 0.76; HR, 8.94; $P < 0.001$

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Conflict of interest

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vs D'Amico C-index, 0.70; HR, 4.67; $P < 0.001$) and showed incremental improvement over the 10-year postoperative nomogram (C-index, 0.75; HR, 5.83; $P < 0.001$).

- The postoperative tissue model provided additional risk discrimination over surgical margin status and extracapsular extension for predicting disease outcome, and was most significant for the clinical (systemic) failure endpoint (surgical margin: C-index, 0.58; HR, 1.57; $P = 0.2$; extracapsular extension: C-index, 0.62; HR, 2.06; $P = 0.04$).
- Risk assessment models that incorporate characteristics from the patient's own tumour specimen are more accurate than clinical-only nomograms for predicting significant disease outcome.
- Systems-based tools should provide useful information concerning the appropriate receipt of adjuvant therapy in the post-surgical setting.

Keywords

prostate cancer; systems-based models; nomogram

Introduction

The impact of a positive surgical margin on disease outcome is controversial primarily as a result of conflicting reports in the literature with respect to an association with biochemical recurrence and/or distant metastasis [1–4]. Recent evidence suggests that these discrepancies may be based, in part, on the patients individual level of risk. For low-risk patients (Gleason score, GS, ≤ 6 , PSA level ≤ 10 ng/mL), the disease course is the same regardless of margin status, whereas margin status remains an independent predictor of biochemical recurrence for intermediate (GS = 7 or PSA level in the range 10–20 ng/mL) and high-risk (GS ≥ 8 or PSA level > 20 ng/mL) patients [5]. Nevertheless, the clinical dilemma remains; once a positive margin is diagnosed, both the surgeon and patient experience a certain degree of uncertainty with respect to treatment options and expected future outcome [6]. Some urologists rely on clinical outcome models including nomograms to understand the importance of a positive margin; however, the reliance on a biochemical recurrence endpoint as a measure of significant outcome and the association of margin status more with the technical skill of the surgeon and not as a surrogate for cancer control, has challenged this view [7,8].

The improved overall survival results from a long-term follow-up randomized clinical trial on the use of the receipt of adjuvant therapy for pathological T3N0M0 prostate cancer has increased the clinical importance of a more accurate risk assessment as part of the overall treatment plan for the surgical patient [9]. Furthermore, given the risk associated with the receipt of adjuvant therapy (bladder stricture, bone loss), it is critically important for the urologist to incorporate the most accurate clinical tools when determining the likelihood of disease outcome. This is further complicated by two recent retrospective population-based studies that differ in their conclusion regarding the association of a positive surgical margin and prostate cancer-specific and overall survival [7,10]. These studies emphasize the importance of establishing a defined and comprehensive risk strategy for all patients with prostate cancer, either at diagnosis or post-treatment. We previously observed that, although

margin status was selected in a multivariate model for predicting PSA recurrence (PSAR), when additional patients were included in the final analysis, extracapsular extension (ECE) replaced margin status for predicting progression [11]. Indeed, the only clinical–pathological variable associated with prostate cancer survival in a randomized clinical trial comparing monitoring with radical prostatectomy was ECE, and not margin status, suggesting the more biological significance of this endpoint [12].

The present study further explores the incorporation of a multidimensional clinical tool to assist in defining a baseline phenotype useful for future clinical decision-making. Furthermore, we evaluate and compare the use of the systems-based approach with respect to patient stratification by individual risk groups, a postoperative (nomogram) calculator [13] and selective pathological features, at the same time as emphasizing the importance of having a complete understanding of the overall clinical disease state in the therapeutic decision process.

Patients and methods

The study was approved by the institutional review board of Memorial Sloan-Kettering Cancer Center. We utilized clinical data and prostatectomy specimens from our original study cohort consisting of men treated with radical prostatectomy at Memorial Sloan-Kettering Cancer Center between 1985 and 2003 for localized and locally advanced prostate cancer [11]. The analytic tissue approach included a morphometric haematoxylin and eosin image analysis and multiplex immunofluorescence to extract quantitative features from the patient's prostatectomy specimens. A detailed account of the specific methods and analysis platform has been reported previously [11,16]. The original cohort consisted of 881 post-prostatectomy patients randomized and evenly split between training and validation sets. For the present analysis, we focused on 373 training set patients with complete clinical data and developed two independent prognostic models that integrate clinical variables with prostatectomy tissue features, including haematoxylin and eosin morphometry and quantitative immunofluorescence of several markers (e.g. androgen receptor and α -methyl coenzyme A-racemase). The integration of high dimensional and complex data, including patients whose outcome was unknown or censored, was performed with support vector regression for censored data (SVRc) [11]. Our experience with SVRc has shown that this approach can increase the predictive accuracy of a model over that of the Cox model.

The biopsy GS, preoperative PSA, surgical margin status (SM), ECE and the time-dependent systems model prognostic scores (PX) for both PSAR and clinical failure (CF) were collected from patients in the training cohort ($n = 373$). PSAR was defined as two consecutive PSA measurements >0.2 ng/mL post-surgery and CF consisted of a composite endpoint that included a rising PSA in a castrate state, castrate or non-castrate systemic disease including bone metastasis, or death attributed to prostate cancer. The time to CF was defined as the time from radical prostatectomy to the first of these events. In addition to PX probability, patients were stratified by standard risk groups according to the D'Amico classification (i.e. low risk, PSA < 10 ng/mL, T1c–T2a, GS ≤ 6 ; intermediate risk, PSA 10–20 ng/mL, T2b–c, GS 7 and high risk, PSA > 20 ng/mL, T3a or GS ≥ 8) [14,15]. The predictive accuracy of SM, ECE, PS and standard risk groups for stratifying patients as low/

high risk for PSAR and CF was determined using the concordance index (C-index) and hazard ratio (HR). In addition, all patients were stratified using the postoperative variables in the Kattan 10-year PSAR nomogram [13].

Results

Because of incomplete outcome data, 342 of the 373 patients in the original training cohort were included in the PSAR models and all 373 patients were utilized in the CF group. The complete demographic breakdown for the individual training cohorts has been reported previously [11,16]. Both groups exhibited comparable clinical features, including 60% patients pT2, 32% with prostatectomy GS = 6, 56% with GS = 7 and 65% with a preoperative PSA < 10 ng/mL. The overall positive SM and ECE rate for the PSAR group was 36% and 28%, respectively. By comparison, the positive SM and ECE rate for the CF group was 37% and 7%, respectively. Between the PSAR and CF training groups, there was a relatively even distribution of low-risk (126 vs 127), intermediate-risk (116 vs 129) and high-risk (100 vs 117) patients based on D'Amico criteria [14,15].

We compared the ability to predict PSAR and CF with the PX, D'Amico and nomogram criteria. Survival analysis using the log-rank test showed that PX improved patient stratification over traditional risk group classification or the nomogram for predicting either PSAR (C-index, 0.76, HR, 8.94, $P < 0.001$ vs C-index, 0.70 [high-risk group], HR, 4.67, $P < 0.001$ and C-index, 0.75, HR, 5.83, $P < 0.001$; Figs 1A–C) or CF (CI, 0.84, HR, 17.46, $P < 0.001$ vs C-index, 0.73 [high-risk group], HR, 11, $P = 0.001$ and C-index, 0.79, HR, 5.06, $P < 0.001$; Figs 2A–C), although the difference between the PX and the 10-year nomogram for predicting PSAR was limited but incremental. Furthermore, when we examined only SM or ECE status across the entire cohort, survival analysis showed an improvement with PX low/high risk classification over SM or ECE alone (SM PSAR CI, 0.61, HR, 2.49, $P < 0.001$, Fig. 3A; ECE PSAR, CI, 0.61, HR, 2.78, $P < 0.001$, Fig. 3B; SM CF CI, 0.58, HR, 1.57, $P = 0.2$, Fig. 3C; ECE CF CI, 0.62, HR, 2.06, $P = 0.04$, Fig. 3D) (Table 1).

Because of the observed overall improvement of predictive accuracy with PX models, we then assessed the impact of a positive SM or ECE for PSAR and CF within the traditional standard risk groups and PX risk categories. The SM and ECE rate increased between the standard risk groups, with similar trends observed in the PX low- and high-risk categories for both endpoints. Of interest, the most significant change was noted for ECE rate between low- and high-risk groups in the PX PSAR model (17% vs 51%) and, as previously reported, only ECE and not SM was selected in the PX PSAR multivariate model [11]. For the standard risk categories, only in the intermediate risk group was SM and ECE associated with PSAR outcome, with a higher significance noted for ECE (ECE HR, 8.44, $P = 0.001$ vs SM HR, 6.88, $P = 0.02$). Neither SM, nor ECE were associated with CF in the standard risk categories. For the PX models, only ECE status in the PX low-risk group was marginally associated with PSAR (HR, 3.12, $P = 0.046$) and neither SM, nor ECE were associated with CF in either the PX low- or high-risk groups.

Discussion

Clinical decisions should be based on a thorough understanding of the role individual variables play in defining risk for a particular disease outcome. It is for this reason that the prostate cancer oncology practice guidelines (National Comprehensive Cancer Network, version 2.2010) recommend the incorporation of integrative risk stratification tools in the treatment decision process. By evaluating and interconnecting discordant variables, we are able to understand the collective importance of the clinical state of disease. This is especially important for urologists who are managing patients with prostate cancer treated with surgery (i.e. the ability to identify the important post-treatment risk factors to provide maximum cancer control). Several studies have highlighted the conflicted importance of margin status alone for predicting significant disease progression [7,10]. A recent retrospective study on a large patient cohort ($n = 2468$) showed that margin status, either focal or extensive, and in conjunction with the prostatectomy GS, increased the risk for biochemical recurrence, even in patients with organ-confined disease [16]. Furthermore, Stephenson *et al.* [18] showed that men with a positive surgical margin and associated ECE were at increased risk for PSAR, suggesting that additional factors provide useful information for determining an outcome.

In the current iteration of the various clinical prognostic tools, margin status continues to play an important role for predicting outcome, especially when combined with additional clinical–pathological attributes. The data obtained in the present study would suggest that multivariate modelling approaches incorporating biological parameters from the actual tumour specimen will further discriminate clinical disease states and provide a valuable tool for weighing clinical features with respect to outcome and use of the receipt of adjuvant therapy. This approach appears to be particularly beneficial for predicting significant disease outcomes, such as the time to disease progression events post-treatment failure, as shown in the present study. Furthermore, it is worth noting the comparable results between the 10-year postoperative nomogram and the systems models for predicting PSAR, despite the difference in the definition of PSAR between the two studies (i.e. Kattan 10-year is a serum PSA level ≥ 0.4 ng/mL, confirmed by a second measurement that was higher than the first by any amount vs two consecutive PSA levels > 0.2 ng/mL). The clinical importance of preventing biochemical relapse with the receipt of early adjuvant radiotherapy in more pathologically advanced disease has been reported previously [19]. Similar results were observed in a long-term outcome randomized clinical trial where the receipt of adjuvant radiotherapy increased metastasis-free and overall survival in comparable patients [5,20]. Furthermore, a recently reported retrospective analysis showed a survival benefit for postoperative radiotherapy in patients with organ confined, margin-positive prostate cancer [21]. The results of the present study are in agreement with a previous study that noted the importance of margin status with biochemical relapse in intermediate- and high-risk categories [5]. We expanded upon this original observation to include stage in the definition of risk and examined the association of both SM and ECE with a more clinically significant endpoint (i.e. systemic disease progression). As independent variables, SM and ECE were only slightly associated with clinically significant disease and not associated when evaluated within the individual standard risk groups or PX. This observation supports the inherent

limitations when using a single feature (e.g. SM or ECE) for determining clinical outcome and indicates that more complete and comprehensive analyses are necessary.

For the PX models in particular, the predicted time frame of 5 years after surgery and the individual selected features appear to identify a biologically significant phenotype for both PSAR and CF that is potentially important for early intervention. Of note, Walz *et al.* [22] reported that a GS ≥ 7 , seminal vesicle invasion and lymph node status were associated with an early (within 2 years) biochemical recurrence and suggested that such patients may derive the most benefit from receipt of adjuvant treatment. By comparison, of the three clinical features noted, only seminal vesicle invasion was selected in the multivariate PX PSAR model. The additional PX PSAR variables include the dominant prostatectomy Gleason grade, biopsy Gleason score, PSA level and biometric attributes of the prostatectomy specimen. Interestingly, SM was not selected in the PX PSAR model and the only clinical variables in the PX CF model were lymph node status and the dominant prostatectomy grade. This differential association of specific clinical features with respect to outcome within the two PX models would suggest a discrimination of clinical disease states and an alignment with biological (growth) mechanisms [15]. We consider this to be an important distinction because many predictive models provide apparently comparable statistical significance, as shown in the present study for the PSAR PX vs nomogram stratification; however, it is the composition and weight of the predictive variables combined with the biology within the patient's tumour specimen that is necessary for appropriate patient-specific risk discrimination. There are limitations to the present analysis, most notably the retrospective study design, and therefore future efforts are in progress aiming to assess the impact in randomized clinical trials evaluating the receipt of adjuvant therapy and reported outcome. An additional question surrounds the comparison of postoperative models with preoperative standard risk groups because the prostatectomy models are traditionally considered to be more robust. The standard risk groups (D'Amico) as applied in the present analysis are identical to those used and recommended by the American Urological Association for stratifying patients when predicting disease outcomes. We included the 10-year postoperative nomogram to be comprehensive in our comparison analysis.

In conclusion, we have confirmed the importance of applying risk stratification for significant disease progression after surgery. In addition, by integrating features from the patient's prostatectomy specimen with clinical variables, as reported in the PX models, we have been able to provide a more accurate tool for determining significant risk than either standard risk groups, a clinical 10-year postoperative nomogram, and SM or ECE alone.

Abbreviations

CF	clinical failure
C-index	concordance index
ECE	extracapsular extension
GS	Gleason score
HR	hazard ratio

PSAR	PSA recurrence
PX	prognostic score
SM	surgical margin status
SVRc	support vector regression for censored data

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A.

B.

C.

FIG. 1.

Kaplan–Meier survival curves for probability of remaining free of PSA recurrence (PSAR) (A–C) among patients from the postoperative model training cohort, dichotomized by risk and stratified by score in the support vector regression for censored data (SVRc) prognostic score (PX) model (A), D’Amico/AUA risk groups (B) and comparison of SVRc (PX) model (score) with the 10-year postoperative nomogram (C). A, Blue solid line indicates low predicted risk (PSAR PX model score ≤ 41); red dashed line indicates high predicted risk (PSAR PX model score > 41). B, blue line indicates low risk, green line indicates intermediate risk and red line indicates high risk. C, Blue solid line indicate PX risk group and blue dashed line indicates nomogram low risk; red solid line indicates PX model score high risk and red dashed line indicates nomogram high risk. The probability of remaining free of clinical progression is provided on the y-axis and the follow-up time (months) is given on the x-axis. An optimal threshold was determined for each clinical variable according to the log-rank test ($P < 0.001$).

A.

B.

FIG. 2.

Kaplan–Meier survival curves for probability of remaining free of clinical (systemic) failure (CF model) (A–C) among patients from the postoperative model training cohort, dichotomized by risk and stratified by score in the support vector regression for censored data (SVRc) prognostic score (PX) model (A), D’Amico/AUA risk groups (B) and comparison of SVRc (PX) model (score) with the 10-year postoperative nomogram. A, Blue solid line indicates low predicted risk (CF PX model score ≤ 30.19); red dashed line indicates high predicted risk (CF PX model score > 30.19). B, blue line indicates low risk, green line indicates intermediate risk and red line indicates high risk. C, blue solid line indicate PX risk group and blue dashed line indicates nomogram low risk; red solid line indicates PX model score high risk and red dashed line indicates nomogram high risk. The probability of remaining free of clinical progression is provided on the y-axis and follow-up time (months) is given on the x-axis. An optimal threshold was determined for each clinical variable according to the log-rank test ($P < 0.001$).

A.

B.

C.

D.

FIG. 3.

Kaplan–Meier survival curves for probability of remaining free of PSA recurrence (**A, B**) or clinical (systemic) failure (CF model) (**C, D**) among patients in the postoperative training cohort, dichotomized by risk and stratified by either a (positive) surgical margin (SM) or extracapsular extension (ECE). Blue lines indicate a low-risk group; red lines indicate high-risk groups. An optimal threshold was determined for each clinical variable according to the log-rank test ($P < 0.001$).

TABLE 1

Comparison of postoperative model prognostic score (PX) with surgical margin (SM) and extracapsular extension (ECE) for predicting PSA recurrence (PSAR) and clinical failure (CF)

Prediction	PX	SM	ECE
PSAR	CI, 0.76; HR, 8.94; $P < 0.001$,	CI, 0.61; HR, 2.49; $P < 0.001$	CI, 0.61; HR, 2.78; $P < 0.001$
CF	CI, 0.84; HR, 17.46; $P < 0.001$	CI, 0.58; HR, 1.57; $P = 0.2$	CI, 0.62; HR, 2.06; $P = 0.04$

CI, C-index; HR, hazard ratio.